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(54) Title: **DIAMINO-FUNCTIONAL CHALCONES**

(57) Abstract: The invention provides novel diamino-functionalised chalcone derivatives and analogues thereof. Use of the compounds, or compositions comprising them, as pharmaceutically active agents, in particular against bacterial and parasitic infections, is also disclosed. The invention further relates to a method for detecting inhibitory effects against e.g., bacteria, parasites, fungi, and helminths. The chalcones of the invention carry amino substituents and exhibit enhanced biological effects combined with improved metabolic and physicochemical properties, making the compounds useful as drug substances, in particular as antiparasitic and bacteriostatic agents.

DIAMINO-FUNCTIONAL CHALCONES

FIELD OF THE INVENTION

The present invention relates to a novel class of chalcone derivatives and analogues and to their use as pharmaceutically active agents, in particular against bacterial and parasitic
5 infections.

Furthermore, the invention relates to a method of predicting whether a chemical compound has a potential inhibitory effect against an organism such as *Helicobacter pylori* and *Plasmodium falciparum*. The prediction is based on the ability of the chemical
10 compound to act as an inhibitor of the enzyme dihydroorotate dehydrogenase which is involved in the synthesis of pyrimidine in prokaryotic as well as eukaryotic cells such as bacteria, parasites, fungi, helminths and any type of mammalian cells such as human cells.

BACKGROUND OF THE INVENTION

15 Chalcones, e.g., for use against parasitic infections are known from earlier patent applications assigned to the applicant, e.g. WO 93/17671 and WO 99/00114. Moderate antibacterial activity has been reported for a limited number of chalcones in earlier publications e.g. Haraguchi, H. et al *Phytochemistry* 1998, 48, 125-129 and Hatano, T. et al *Chem. Pharm. Bull (Tokyo)* 2000, 48, 1286-92.

20 The bioavailability of the known, neutral chalcones is low/not detectable due to the low solubility of the compounds. The compounds do not typically dissolve in the intestine and are therefore not available for absorption.

25 The spread of antimicrobial resistance determinants particular among nosocomial bacterial pathogens is an increasing problem. Such resistant pathogens include *Staphylococcus aureus* resistant to methicillin and thus to all β -lactam-antibiotics and Enterococci resistant to vancomycin (VRE). Such resistant bacteria pose a significant therapeutic challenge and bacterial strains resistant to all currently available antimicrobials are emerging.

30 Furthermore, bacterial species intrinsically resistant to commonly employed antimicrobials are being recognized as important opportunistic pathogens in the setting of long-term immunocompromized patients. An example of this is *Stenotrophomonas maltophilia* which possesses a β -lactamase rendering the bacteria intrinsically resistant to carbapenems. As cross-resistance within a given class of antibiotics often occurs the development of new
35 classes of antibiotics is a necessity to counter the emerging threat of bacterial resistance.

The resistance of *Plasmodium falciparum* to chloroquine and other antimalarial drugs have created an urgent need for new drugs that are safe and effective for the prophylaxis and treatment of malaria.

Furthermore, the increasing appearance of resistance to first line antileishmanial drugs, e.g. Pentostam or Glucantime, emphasizes the need for new drugs for the treatment of *Leishmania* infections.

- 5 Thus, there is a need for chalcone derivatives with improved therapeutic or prophylactic activity against parasites and bacteria.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 illustrates the general synthetic scheme for the preparation of diamino-functional chalcones where the aromatic rings are phenyl rings. $R^4 = H$ (yielding the B ring) or CH_3
10 (yielding the A ring); R^1 , R^2 , R^3 and Z are as defined herein.

Figure 2 illustrates the scheme for the preparation of diamino (aminoacylamino)-functional chalcones where the aromatic rings are phenyl. R^1 , R^2 and R^3 are as defined herein, $R^4 = H$ or CH_3 , and $Y = (C(R^H)_2)_{n-1}$.
15

Figure 3 illustrates the synthesis of diamino-dihydrochalcones. R^1 , R^2 , R^3 and Z are as defined herein.

Figure 4 illustrates a time-kill curve of B143 against *S.aureus* ATCC29213. Bacterial growth
20 is inhibited at concentrations at or above the MIC (MIC=9.4 μM). As CFU counts per ml decreases at concentrations of compound above the MIC, the compound is bactericidal. The reduction in CFU/ml is faster as the concentration of test compound increases above the MIC. This indicates that the bactericidal action of the compound is primarily dependent on the concentration of the test compound.

Figure 5 illustrates a time-kill curve of B041 against *S.aureus* ATCC29213. Bacterial growth
25 is inhibited at concentrations of test compound at or above the MIC (MIC=9.4 μM). As CFU counts per ml decreases at concentrations of compound above the MIC, the compound is bactericidal. The rate of reduction of CFU/ml is not significantly affected by increasing
30 concentrations of test compound. Thus, the bactericidal action of the compound is primarily dependent on incubation time.

Figure 6 illustrates a dose-respons curve of Licochalcone A (LicA) and one of the novel diamino-chalcones B118 at *Plasmodium falciparum*. As shown at the figure, B118 is 40
35 times more potent than LicA.

Figure 7 illustrates a dose-respons curve of LicA and one of the novel diamino-chalcones B047 at *Leishmania Major*. As shown at the figure, B047 is 10 times more potent than LicA.

Figure 8 illustrates an effect curve of B119 in *Plasmodium berghei* K173 infected NMRI female mice following multiple oral administrations. As shown at the figure, treatments
40 with these chalcones inhibit the development of the infection.

Figure 9 illustrates the effect of B208 on mice infected with leishmania donovani. Treatment are initiated on Day 0 and are continued for 5 consecutive days. The infection is expressed as Leishmania Donovan Units (LDU): (Mean number of amastigotes per liver or spleen cell) x (mg liver or spleen).

Figure 10 illustrates an effect curve of B074 in *Plasmodium berghei* K173 infected NMRI female mice following multiple intra venous administrations. As shown at the figure, treatment with B074 causes a significant decrease in the parasitaemia.

DESCRIPTION OF THE INVENTION

The present inventors have found that the diamino-functional chalcones defined herein exhibit interesting biological properties combined with improved metabolic and physicochemical properties which make the compound useful as drug substances, in particular as antiparasitic agents, bacteriostatic agents, and bacteriocidal agents.

It is believed that the diamino group or groups of the diamino-functional chalcone will be charged according to pH of the medium and the pKa of the compound. The solubility of the charged compounds is many times higher than the solubility of the neutral compounds. As the diamino-functional chalcones will be partially charged (i.e. soluble) at the pH in the intestine, they will dissolve in the gastric juices and be available for absorption. The bioavailability of the diamino-functional chalcones will therefore be improved many times compared to the known neutral chalcones making the compounds generally useful as drug candidates. Also, the diamino-functional chalcones have different pKa values which enable the selection of a chalcone derivative with optimal *charged/non-charged* ratio at a given pH value.

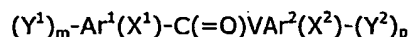
The usefulness of the known chalcones as drug candidates have been limited by the metabolism of the compounds resulting in short half-lives *in vivo*. The inventors have now found that introduction of a diamino group in the chalcone derivative changes the metabolic properties and the compounds prepared show improved metabolic stability.

The introduction of an aliphatic amino-group and hence a positive charge (at the pH value of the target site) affects the mode of interaction with the biological target. It is anticipated that the compounds interact with the target in a different way than neutral chalcones, due to the possibility of strong electrostatic interactions (attraction as well as repulsion). This is indeed reflected in the activity of the compounds, being more potent than the previously described neutral chalcones.

Of particular interest, the present inventors have found that the amino-functional chalcones defined herein are far more potent against malaria and leishmania parasites

than the earlier described neutral chalcone compounds, and that they exhibit excellent bacteriocidal and bacteriostatic properties, even against multi-resistant bacteria strains.

Thus, the present invention provides chalcone derivatives and analogues as defined in
5 claim 1, i.e. a compound of the general formula:



wherein Ar^1 and Ar^2 independently may be selected from aryl or heteroaryl;

10

V designates $-CH_2-CH_2-$, $-CH=CH-$ or $-C\equiv C-$, preferably $-CH=CH-$;

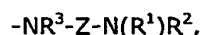
m is 0, 1, or 2,

15 p is 0, 1, or 2,

wherein the sum of m and p is at least 1;

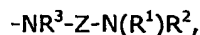
each Y^1 independently represents a diamino-functional substituent of the formula

20



each Y^2 independently represents a diamino-functional substituent of the formula

25



wherein Z is a biradical $-(C(R^H)_2)_n-$, wherein n is an integer in the range of 1-6, preferably 2-4, such as 2-3, and each R^H may independently be selected from hydrogen or C_{1-6} -alkyl, or two R^H on the same carbon atom may designate =O;

30

R^1 and R^2 may independently be selected from hydrogen, optionally substituted C_{1-12} -alkyl, optionally substituted C_{2-12} -alkenyl, optionally substituted C_{4-12} -alkadienyl, optionally substituted C_{6-12} -alkatrienyl, optionally substituted C_{2-12} -alkynyl, optionally substituted C_{1-12} -alkoxycarbonyl, optionally substituted C_{1-12} -alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroarylcarbonyl, aminocarbonyl, mono- and di(C_{1-6} -alkyl)aminocarbonyl, amino- C_{1-6} -alkyl-aminocarbonyl, or mono- and di(C_{1-6} -alkyl)amino- C_{1-6} -alkyl-aminocarbonyl; or R^1 and R^2 together with the nitrogen atom to which they are attached ($-N(R^1)R^2$) form an

35 optionally substituted nitrogen-containing heterocyclic ring;

R^3 may be selected from hydrogen, C_{1-6} -alkyl, or C_{1-6} -alkylcarbonyl, said alkyl and alkylcarbonyl optionally carrying substituent(s) selected from halogen, hydroxy, C_{1-6} -alkoxy, carboxy, C_{1-6} -alkoxycarbonyl, C_{1-6} -alkylcarbonyl, amino, mono- and di(C_{1-6} -alkyl)amino, or aryl, optionally substituted 1-3 times with C_{1-4} -alkyl, C_{1-4} -alkoxy, nitro,

40

cyano, amino or halogen; or R^1 and R^3 together form a biradical Z^* which is as defined for Z ;

- X^1 and X^2 may independently designate 0-5, preferably 0-4, such as 0-3, e.g. 0-2, 5 substituents, where such optional substituents may independently be selected from optionally substituted C_{1-12} -alkyl, optionally substituted C_{2-12} -alkenyl, optionally substituted C_{4-12} -alkadienyl, optionally substituted C_{6-12} -alkatrienyl, optionally substituted C_{2-12} -alkynyl, hydroxy, optionally substituted C_{1-12} -alkoxy, optionally substituted C_{2-12} -alkenyloxy, carboxy, optionally substituted C_{1-12} -alkoxycarbonyl, optionally substituted C_{1-12} -alkylcarbonyl, formyl, C_{1-6} -alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted aryloxy, optionally substituted arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroaryloxy, optionally substituted heteroarylcarbonyl, optionally substituted heteroarylamino, heteroarylsulphonylamino, optionally substituted heterocyclyl, optionally substituted heterocyclyloxycarbonyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylcarbonyl, optionally substituted heterocyclylamino, heterocyclylsulphonylamino, amino, mono- and di(C_{1-6} -alkyl)amino, carbamoyl, mono- and di(C_{1-6} -alkyl)aminocarbonyl, amino- C_{1-6} -alkyl-aminocarbonyl, mono- and di(C_{1-6} -alkyl)amino- C_{1-6} -alkyl-aminocarbonyl, C_{1-6} -alkylcarbonylamino, amino- C_{1-6} -alkyl-carbonylamino, mono- and di(C_{1-6} -alkyl)amino- C_{1-6} -alkyl-carbonylamino, cyano, guanidino, carbamido, C_{1-6} -alkanoyloxy, C_{1-6} -alkylsulphonyl, C_{1-6} -alkylsulphanyl, C_{1-6} -alkylsulphonyloxy, aminosulfonyl, mono- and di(C_{1-6} -alkyl)aminosulfonyl, nitro, optionally substituted C_{1-6} -alkylthio, or halogen, where any nitrogen-bound C_{1-6} -alkyl may be substituted with 25 hydroxy, C_{1-6} -alkoxy, C_{2-6} -alkenyloxy, amino, mono- and di(C_{1-6} -alkyl)amino, carboxy, C_{1-6} -alkylcarbonylamino, halogen, C_{1-6} -alkylthio, C_{1-6} -alkyl-sulphonyl-amino, or guanidine;

and salts thereof.

- 30 The substituents R^1 and R^2 carried by the one nitrogen atom of the diamino substituent, and R^3 carried by the other nitrogen atom of the diamino substituent are believed to slightly alter the pKa value of the chalcone derivative. Thus, the particular selection of the groups R^1 , R^2 and R^3 may be used to fine-tune the pKa value in view of the particular condition or disease and the intended route of administration.

35

- In one embodiment, R^1 and R^2 may independently be selected from hydrogen, optionally substituted C_{1-12} -alkyl, optionally substituted C_{2-12} -alkenyl, optionally substituted C_{2-12} -alkynyl, optionally substituted C_{1-12} -alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, aminocarbonyl, mono- and di(C_{1-6} -alkyl)aminocarbonyl, amino- C_{1-6} -alkyl-aminocarbonyl, and 40 mono- and di(C_{1-6} -alkyl)amino- C_{1-6} -alkyl-aminocarbonyl. In particular R^1 and R^2 are independently selected from hydrogen, optionally substituted C_{1-6} -alkyl, optionally substituted C_{1-6} -alkylcarbonyl, heteroarylcarbonyl, aminocarbonyl, mono- and di(C_{1-6} -alkyl)aminocarbonyl, amino- C_{1-6} -alkyl-aminocarbonyl, or mono- and di(C_{1-6} -alkyl)amino- C_{1-6} -alkyl-aminocarbonyl.

In another embodiment, R^1 and R^2 , together with the nitrogen atom to which they are attached ($-N(R^1)R^2$), may form an optionally substituted nitrogen-containing heterocyclic ring.

5

In a further embodiment, R^3 may be selected from hydrogen or methyl, in particular methyl.

In still a further embodiment, X^1 and X^2 may independently designate 0-4, such as 0-3, e.g. 0-2, substituents, where such optional substituents independently may be selected from optionally substituted C_{1-12} -alkyl, hydroxy, optionally substituted C_{1-12} -alkoxy, optionally substituted C_{2-12} -alkenyloxy, carboxy, optionally substituted C_{1-12} -alkylcarbonyl, formyl, C_{1-6} -alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxy, optionally substituted aryloxy, optionally substituted arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, optionally substituted heteroarylcarbonyl, optionally substituted heteroaryloxy, heteroarylsulphonylamino, optionally substituted heterocyclyl, optionally substituted heterocycloxy, optionally substituted heterocyclylamino, amino, mono- and di(C_{1-6} -alkyl)amino, carbamoyl, mono- and di(C_{1-6} -alkyl)aminocarbonyl, amino- C_{1-6} -alkyl-aminocarbonyl, mono- and di(C_{1-6} -alkyl)amino- C_{1-6} -alkyl-aminocarbonyl, C_{1-6} -alkylcarbonylamino, amino- C_{1-6} -alkyl-carbonylamino, mono- and di(C_{1-6} -alkyl)amino- C_{1-6} -alkyl-carbonylamino, guanidino, carbamido, C_{1-6} -alkylsulphonyl, C_{1-6} -alkylsulphiny, C_{1-6} -alkylsulphonyloxy, optionally substituted C_{1-6} -alkylthio, aminosulfonyl, mono- and di(C_{1-6} -alkyl)aminosulfonyl, or halogen, where any nitrogen-bound C_{1-6} -alkyl may be substituted with hydroxy, C_{1-6} -alkoxy, and/or halogen, in particular, X^1 and X^2 may independently designate 0-3, e.g. 0-2, substituents, where such optional substituents independently may be selected from optionally substituted C_{1-6} -alkyl, hydroxy, optionally substituted C_{1-6} -alkoxy, carboxy, optionally substituted C_{1-6} -alkylcarbonyl, C_{1-6} -alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, heteroarylsulphonylamino, amino, mono- and di(C_{1-6} -alkyl)amino, carbamoyl, C_{1-6} -alkylcarbonylamino, guanidino, carbamido, optionally substituted C_{1-6} -alkylthio, optionally substituted heterocyclyl, optionally substituted heterocycloxy, optionally substituted heterocyclylamino or halogen, where any nitrogen-bound C_{1-6} -alkyl may be substituted with hydroxy, C_{1-6} -alkoxy, and/or halogen.

The group V is relevant with respect to the spatial orientation of the rings Ar^1 and Ar^2 .

Thus, the group V may be $-CH_2-CH_2-$, $-CH=CH-$ or $-C\equiv C-$. In a currently preferred embodiment V designates $-CH=CH-$.

In the context of the present invention the expression "chalcone derivative" has been assigned to the compounds of the above formula in that the overall structure namely $Ar^1-C(=O)-C-C-Ar^2$ resembles that of the chalcone structure. This being said, Ar^1 and Ar^2 are

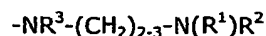
selected from aromatic rings and heteroaromatic rings. It is currently believed that particularly interesting compounds are those where at least one of Ar¹ and Ar², preferably both, are aryl, in particular phenyl. This being said, the inventors envisage that the functionality of the compounds may be substantially preserved (or even improved) when
 5 one or both of Ar¹ and Ar² are heteroaromatic rings.

In one embodiment, at least one of Ar¹ and Ar² is selected from thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, quinolyl, isoquinolyl, and indolyl.
 10
 In another embodiment, both of Ar¹ and Ar² are phenyl rings and Y¹ represent at least one diamino-functional substituent, e. g. m is 1 or 2, and p is 0..

In a further embodiment, X² represents at least one substituent selected from C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, mono- and di(C₁₋₆-alkyl)amino, C₁₋₆-alkylcarbonylamino, optionally substituted C₁₋₆-alkylthio, optionally substituted heterocyclyl, optionally substituted heterocycloxy, optionally substituted heterocyclylamino or halogen, in particular, X²
 15
 20 represents at least two halogen atoms.

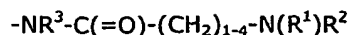
The Z group represents the biradical between the two nitrogen atoms of the diamino functionality. This group Z is typically a biradical -(C(R^H)₂)_n-, wherein n is an integer in the range of 1-6, preferably 2-4, such as 2-3, where each R^H is independently selected from hydrogen and C₁₋₆-alkyl, or two R^H on the same carbon atom may designate =O. A particular example of Z is -(CH₂)_n- wherein n is 2-4, such as 2-3.
 25

Thus, in a particular embodiment, one of Y¹ and Y² represents a substituent of the formula
 30



wherein R³ is selected from hydrogen and methyl, and R¹ and R² are selected from hydrogen and C₁₋₆-alkyl. Furthermore, V is preferably -CH=CH-, and Ar¹ and Ar² are
 35 optionally substituted phenyl.

In a further embodiment, one of Y¹ and Y² represents a substituent of the formula



40 wherein R³ is selected from hydrogen and methyl, and R¹ and R² are selected from hydrogen and C₁₋₆-alkyl. Furthermore, V is preferably -CH=CH-, and Ar¹ and Ar² are optionally substituted phenyl.

In one preferred embodiment, m is 1 and p is 0. In another preferred embodiment m is 0 and p is 1. In a further interesting embodiment, m and p are both 1.

In a still further interesting embodiment, one or both of X¹ and X² may independently
 5 designate one optionally substituted C₁₋₁₂-alkyl group of the formula



wherein A is a biradical $-(C(R^H)_2)_n-$, wherein n is an integer in the range of 1-6, preferably
 10 1-4, such as 1-3, and each R^H is independently selected from hydrogen and C₁₋₆-alkyl, and
 R¹ and R² may independently be selected from hydrogen, optionally substituted C₁₋₁₂-alkyl,
 optionally substituted C₂₋₁₂-alkenyl, optionally substituted C₄₋₁₂-alkadienyl, optionally
 substituted C₆₋₁₂-alkatrienyl, optionally substituted C₂₋₁₂-alkynyl, optionally substituted
 C₁₋₁₂-alkoxycarbonyl, optionally substituted C₁₋₁₂-alkylcarbonyl, optionally substituted aryl,
 15 optionally substituted aryloxycarbonyl, optionally substituted arylcarbonyl, optionally
 substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted
 heteroarylcarbonyl, aminocarbonyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-
 alkyl-aminocarbonyl, or mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-aminocarbonyl; or R^k and
 R^m together with the nitrogen atom to which they are attached (-N(R^k)R^m) may form an
 20 optionally substituted nitrogen-containing heterocyclic ring.

According to the present invention, highly preferred compounds of the general formula
 above may be selected from the group comprising:

25 3-[5-Bromo-2-(4-methyl-piperazin-1-yl)-phenyl]-1-(2-fluoro-4-methoxy-phenyl)-
 propenone,
 3-(2,4-Dichlorophenyl)-1-(4-fluorophenyl)propan-1-one,
 3-[3-(2-Dimethylamino-ethylamino)-phenyl]-1-(4-methoxy-phenyl)-propenone,
 3-(2,4-Dichloro-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-
 30 propenone,
 1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(4-fluoro-phenyl)-propenone,
 3-(2,5-Difluoro-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-
 propenone,
 3-(2-Bromo-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone,
 35 3-(4-Bromo-2-fluoro-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-
 propenone,
 3-[4-(2-Dimethylamino-ethylamino)-phenyl]-1-(4-methoxy-phenyl)-propenone,
 3-(4-Chloro-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone,
 3-(3-Bromo-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone,
 40 4-(3-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-oxo-propenyl)-benzonitrile,
 3-(2,5-Dimethoxy-phenyl)-1-[4-(3-dimethylamino-propylamino)-phenyl]-propenone,
 3-(2,4-Dichloro-phenyl)-1-[4-(3-dimethylamino-propylamino)-phenyl]-propenone,
 3-[4-(2-Dimethylamino-ethylamino)-phenyl]-1-(2,3,4-trimethoxy-phenyl)-propenone,
 3-[4-(2-Dimethylamino-ethylamino)-phenyl]-1-(2-fluoro-4-methoxy-phenyl)-propenone,

- 3-(2,4-Dichloro-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone,
3-(4-Chloro-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone,
3-(2,5-Difluoro-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-
5 propenone,
3-(4-Bromo-2-fluoro-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone,
3-(2-Chloro-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone,
1-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(4-methoxy-phenyl)-propenone,
10 3-(2,4-Dimethoxy-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone,
3-(2,4-Dichloro-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone,
1-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(4-methoxy-phenyl)-propenone,
1-(2,3-Dichloro-phenyl)-3-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone,
15 3-(4-Chloro-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone,
3-(2,4-Dimethoxy-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone,
1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(4-methoxy-phenyl)-propenone,
3-(2,5-Dimethoxy-phenyl)-1-[2-(2-dimethylamino-ethylamino)-phenyl]-propenone,
3-(2,4-Dichloro-phenyl)-1-[2-(2-dimethylamino-ethylamino)-phenyl]-propenone,
20 1-[4-(3-Dimethylamino-propylamino)-phenyl]-3-(4-fluoro-phenyl)-propenone,
3-(2,5-Dimethoxy-phenyl)-1-[2-(3-dimethylamino-propylamino)-phenyl]-propenone,
3-(2,5-Dimethoxy-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone,
3-(3-Dibutylamino-phenyl)-1-[2-(3-dimethylamino-propylamino)-phenyl]-propenone,
25 1-[2-(3-Dimethylamino-propylamino)-phenyl]-3-(3-dipropylamino-phenyl)-propenone,
1-[2-(2-Dimethylamino-ethylamino)-phenyl]-3-(3-dipropylamino-phenyl)-propenone,
3-(2,4-Dimethoxy-phenyl)-1-[2-(3-dimethylamino-propylamino)-phenyl]-propenone,
3-(2,4-Dimethoxy-phenyl)-1-[2-(2-dimethylamino-ethylamino)-phenyl]-propenone,
3-(5-Dibutylamino-2-methoxy-phenyl)-1-[2-(2-dimethylamino-ethylamino)-phenyl]-
30 propenone,
3-(2,4-Dichloro-phenyl)-1-[3-(2-dimethylamino-ethylamino)-phenyl]-propenone,
3-[5-(1,1-Dimethyl-allyl)-2-methoxy-phenyl]-1-[4-(3-dimethylamino-propylamino)-phenyl]-propenone,
3-(3-Dibutylamino-phenyl)-1-[2-(2-dimethylamino-ethylamino)-phenyl]-propenone,
35 3-(2,4-Dimethoxy-phenyl)-1-[3-(2-dimethylamino-ethylamino)-phenyl]-propenone,
3-(2,5-Dimethoxy-phenyl)-1-[3-(2-dimethylamino-ethylamino)-phenyl]-propenone,
3-(2,4-Dimethoxy-phenyl)-1-{2-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone,
3-(2,5-Dimethoxy-phenyl)-1-{2-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-
40 propenone,
3-(3,5-Bis-trifluoromethyl-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone,
3-(3,5-Dimethoxy-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone,

- 1-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-phenyl-propenone,
 3-(4-Diethylaminomethyl-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-
 propenone,
 3-(3,5-Dimethoxy-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone,
 5 1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-phenyl-propenone,
 3-(4-Diethylaminomethyl-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone,
 1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(2-fluoro-phenyl)-propenone,
 1-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(2-fluoro-phenyl)-propenone,
 3-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2,3,4-trimethoxy-phenyl)-
 10 propenone,
 3-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2-methoxy-phenyl)-propenone,
 3-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2-dimethylaminomethyl-
 phenyl)-propenone,
 3-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2-fluoro-4-methoxy-phenyl)-
 15 propenone,
 1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(4-pyridin-2-yl-phenyl)-
 propenone,
 3-(4-Butyl-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone,
 1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-quinolin-3-yl-propenone,
 20 1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(4-pyridin-2-yl-phenyl)-propenone,
 3-(4-Butyl-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone,
 1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(4-methoxy-biphenyl-3-yl)-propenone,
 3-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-[2-(4-methyl-piperazin-1-
 ylmethyl)-phenyl]-propenone ,
 25 1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-quinolin-3-yl-propenone,
 1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-quinolin-2-yl-propenone,
 1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(4-dimethylamino-phenyl)-propenone,
 1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(4-imidazol-1-yl-phenyl)-propenone,
 3-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-
 30 propenone,
 1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-{3-[(2-dimethylamino-ethyl)-methyl-
 amino]-phenyl}-propenone,
 1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(2-dimethylaminomethyl-phenyl)-
 propenone,
 35 1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(4-methoxy-biphenyl-3-yl)-
 propenone,
 3-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2-dimethylaminomethyl-
 phenyl)-propenone,
 1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(2-dimethylaminomethyl-phenyl)-
 40 propenone,
 3-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-[2-(4-methyl-piperazin-1-
 ylmethyl)-phenyl]-propenone,
 1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(2-dimethylaminomethyl-
 phenyl)-propenone,

- 1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(4-imidazol-1-yl-phenyl)-propenone,
1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(4-phenoxy-phenyl)-propenone,
3-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2-dimethylaminomethyl-phenyl)-propenone,
5 1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(3-phenoxy-phenyl)-propenone,
1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(3-morpholin-4-ylmethyl-phenyl)-propenone,
1-(2-Fluoro-4-methoxy-phenyl)-3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
10 1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-[3-(pyridin-3-ylamino)-phenyl]-propenone,
3-(4-Diethylamino-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone,
15 1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-quinolin-2-yl-propenone,
N-{3-[3-(2,5-Dimethoxy-phenyl)-acryloyl]-phenyl}-2-dimethylamino-acetamide,
N-{3-[3-(4-Dibutylamino-phenyl)-acryloyl]-phenyl}-2-dimethylamino-acetamide,
3-(2,4-Dichlorophenyl)-1-{4-[(2-dimethylamino-ethyl)methylamino]phenyl}-propan-1-one,
20 3-{3-[4-(2-Methoxy-acetyl)-piperazin-1-yl]-phenyl}-1-(4-methoxy-phenyl)-propenone,
N-{3-[3-(2,4-Dichloro-phenyl)-acryloyl]-phenyl}-2-dimethylamino-acetamide,
N-{3-[3-(4-Dibutylamino-phenyl)-acryloyl]-phenyl}-2-(4-methyl-piperazin-1-yl)-acetamide,
25 1-(3-Dimethylaminomethyl-phenyl)-3-[2'-methoxy-3-(4-methyl-piperazin-1-yl)-biphenyl-4-yl]-propenone,
1-(2-Dimethylaminomethyl-phenyl)-3-[2'-methoxy-3-(4-methyl-piperazin-1-yl)-biphenyl-4-yl]-propenone,
N-{4-[3-(2,4-Dichloro-phenyl)-acryloyl]-phenyl}-*N*-(2-dimethylamino-ethyl)-acetamide,
30 1-(3-Dimethylaminomethyl-4-hydroxy-phenyl)-3-[2'-methoxy-3-(4-methyl-piperazin-1-yl)-biphenyl-4-yl]-propenone,
1-(2-Dimethylaminomethyl-4-methoxy-phenyl)-3-[6-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
1-(3-Dimethylaminomethyl-4-methoxy-phenyl)-3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
35 1-[3-(2-Dimethylamino-ethylamino)-phenyl]-3-[3',5'-dimethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
1-(2-Dimethylaminomethyl-4-methoxy-phenyl)-3-[3',5'-dimethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
40 1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-{3-[4-(2-methoxy-acetyl)-piperazin-1-yl]-phenyl}-propenone,
3-{3-[4-(2-Dimethylamino-acetyl)-piperazin-1-yl]-phenyl}-1-(3-dimethylaminomethyl-phenyl)-propenone,

- 3-{3-[4-(2-Dimethylamino-acetyl)-piperazin-1-yl]-phenyl}-1-(2-fluoro-4-methoxy-phenyl)-propenone,
 1-(2-Fluoro-4-methoxy-phenyl)-3-[4-(4-methyl-piperazin-1-yl)-biphenyl-2-yl]-propenone,
 1-[3-(2-Dimethylamino-ethylamino)-phenyl]-3-[4-(4-methyl-piperazin-1-yl)-biphenyl-2-yl]-propenone,
 1-(4-Hydroxy-phenyl)-3-[4-(4-methyl-piperazin-1-yl)-biphenyl-2-yl]-propenone,
 1-(3-Dimethylaminomethyl-phenyl)-3-[4-(4-methyl-piperazin-1-yl)-biphenyl-2-yl]-propenone,
 1-(3-Dimethylaminomethyl-4-methoxy-phenyl)-3-[4-(4-methyl-piperazin-1-yl)-biphenyl-2-yl]-propenone,
 1-(2-Dimethylaminomethyl-4-methoxy-phenyl)-3-[5-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
 1-[3-(2-Dimethylamino-ethylamino)-phenyl]-3-[5-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
 1-[3-(2-Dimethylamino-ethylamino)-phenyl]-3-[4-[(2-dimethylamino-ethyl)-methyl-amino]-3',5'-dimethyl-biphenyl-3-yl]-propenone,
 3-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-3',5'-dimethyl-biphenyl-3-yl}-1-(2-dimethylaminomethyl-4-methoxy-phenyl)-propenone,
 1-(2-Amino-phenyl)-3-[3',5'-dimethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
 1-[3-(2-Dimethylamino-ethylamino)-phenyl]-3-(3',5'-dimethyl-4-piperazin-1-yl-biphenyl-3-yl)-propenone,
 1-(2-Dimethylaminomethyl-4-methoxy-phenyl)-3-(3',5'-dimethyl-4-piperazin-1-yl-biphenyl-3-yl)-propenone,
 3-{3-Bromo-5-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2-dimethylaminomethyl-phenyl)-propenone,
 3-{5-[(2-Dimethylamino-ethyl)-methyl-amino]-2'-methyl-biphenyl-3-yl}-1-(2-dimethylaminomethyl-phenyl)-propenone,
 3-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-2'-methyl-biphenyl-4-yl}-1-(2-dimethylaminomethyl-phenyl)-propenone,
 3-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-2'-methyl-biphenyl-4-yl}-1-(3-dimethylaminomethyl-phenyl)-propenone,
 3-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-2'-methyl-biphenyl-4-yl}-1-(3-dimethylaminomethyl-4-hydroxy-phenyl)-propenone,
 3-[5-Bromo-2-(4-methyl-piperazin-1-yl)-phenyl]-1-(2-dimethylaminomethyl-phenyl)-propenone,
 3-[2-Bromo-5-(4-methyl-piperazin-1-yl)-phenyl]-1-(2-dimethylaminomethyl-phenyl)-propenone,
 3-{5-[(2-Dimethylamino-ethyl)-methyl-amino]-2'-methyl-biphenyl-3-yl}-1-(2-dimethylaminomethyl-4-methoxy-phenyl)-propenone,
 3-[3-Bromo-5-(3-dimethylamino-propylamino)-phenyl]-1-(2-dimethylaminomethyl-phenyl)-propenone,
 1-(2-Dimethylaminomethyl-4-methoxy-phenyl)-3-[5-(3-dimethylamino-propylamino)-2'-methyl-biphenyl-3-yl]-propenone,

- 1-(2-Dimethylaminomethyl-phenyl)-3-[2'-methyl-4-(4-methyl-piperazin-1-yl)-biphenyl-2-yl]-propenone,
1-(2-Dimethylaminomethyl-4-methoxy-phenyl)-3-[2'-methyl-4-(4-methyl-piperazin-1-yl)-biphenyl-2-yl]-propenone,
5 1-(2-Dimethylaminomethyl-phenyl)-3-[2'-methyl-5-(4-methyl-[1,4]diazepan-1-yl)-biphenyl-3-yl]-propenone,
1-(2-Dimethylaminomethyl-4-methoxy-phenyl)-3-[2'-methyl-5-(4-methyl-[1,4]diazepan-1-yl)-biphenyl-3-yl]-propenone,
1-(2-Dimethylaminomethyl-phenyl)-3-[2'-methyl-5-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
10 1-(2-Dimethylaminomethyl-4-methoxy-phenyl)-3-[2'-methyl-5-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
1-[3-(2-Dimethylamino-ethylamino)-phenyl]-3-{4-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-2'-methoxy-biphenyl-3-yl}-propenone,
15 1-(2-Fluoro-4-methoxy-phenyl)-3-{4-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-2'-methoxy-biphenyl-3-yl}-propenone,
1-[3-(2-Dimethylamino-ethylamino)-phenyl]-3-[4-(4-methyl-piperazin-1-yl)methyl]-biphenyl-3-yl]-propenone,
1-(2-Fluoro-4-methoxy-phenyl)-3-{2-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-phenyl}-propenone,
20 1-(2-Fluoro-4-methoxy-phenyl)-3-[2-(4-methyl-piperazin-1-yl)-5-pyridin-2-yl-phenyl]-propenone,
3-[4-Chloro-5-(1,1-dimethyl-allyl)-2-methoxy-phenyl]-1-[4-methoxy-2-(4-methyl-piperazin-1-yl)-phenyl]-propenone,
25 3-[2'-Methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-1-[4-methoxy-2-(4-methyl-piperazin-1-yl)-phenyl]-propenone,
3-[4-(4-Acetyl-piperazin-1-yl)-2'-methoxy-biphenyl-3-yl]-1-(2-fluoro-4-methoxy-phenyl)-propenone,
4-{4-Bromo-2-[3-(2-fluoro-4-methoxy-phenyl)-3-oxo-propenyl]-phenyl}-piperazine-1-carboxylic acid tert-butyl ester,
30 4-{3-[3-(2-Fluoro-4-methoxy-phenyl)-3-oxo-propenyl]-2'-methoxy-biphenyl-4-yl}-piperazine-1-carboxylic acid tert-butyl ester,
3-[5-Bromo-2-(4-methyl-[1,4]diazepan-1-yl)-phenyl]-1-(2-fluoro-4-methoxy-phenyl)-propenone,
35 1-(2-Fluoro-4-methoxy-phenyl)-3-[2'-methoxy-4-(4-methyl-[1,4]diazepan-1-yl)-biphenyl-3-yl]-propenone,
1-(2-Dimethylaminomethyl-phenyl)-3-[2'-methyl-4-(4-pyrrolidin-1-yl-piperidin-1-yl)-biphenyl-3-yl]-propenone,
1-(2-Dimethylaminomethyl-phenyl)-3-{2'-methyl-4-[methyl-(1-methyl-piperidin-4-yl)-amino]-biphenyl-3-yl}-propenone,
40 1-(2-Dimethylaminomethyl-phenyl)-3-{4-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-2'-methyl-biphenyl-3-yl}-propenone,
1-(2-Dimethylaminomethyl-phenyl)-3-{4-[(3-dimethylamino-propyl)-methyl-amino]-2'-methyl-biphenyl-3-yl}-propenone,

- 3-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-2'-methyl-biphenyl-3-yl}-1-(2-dimethylaminomethyl-phenyl)-propenone,
N-(2-{3-[3',5'-Dimethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-acryloyl}-phenyl)-benzenesulfonamide,
- 5 Propane-1-sulfonic acid (2-{3-[3',5'-dimethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-acryloyl}-phenyl)-amide,
N-(2-{3-[3',5'-Dimethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-acryloyl}-phenyl)-methanesulfonamide,
3-(5-tert-Butyl-2-methoxy-phenyl)-1-[2-fluoro-6-(4-methyl-piperazin-1-yl)-phenyl]-
- 10 propenone,
3-[3',5'-Dimethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-1-[2-fluoro-6-(4-methyl-piperazin-1-yl)-phenyl]-propenone,
1-[2,6-Bis-(4-methyl-piperazin-1-yl)-phenyl]-3-(3-dibutylamino-phenyl)-propenone,
1-[2,4-Bis-(4-methyl-piperazin-1-yl)-phenyl]-3-(3-dibutylamino-phenyl)-propenone,
- 15 3-(3-Dibutylamino-phenyl)-1-[2-fluoro-6-(4-methyl-piperazin-1-yl)-phenyl]-propenone,
1-[2,4-Bis-(4-methyl-piperazin-1-yl)-phenyl]-3-[5-bromo-2-(4-methyl-piperazin-1-yl)-phenyl]-propenone,
1-[2,4-Bis-(4-methyl-piperazin-1-yl)-phenyl]-3-[3',5'-dimethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
- 20 1-[2,4-Bis-(4-methyl-piperazin-1-yl)-phenyl]-3-(5-tert-butyl-2-methoxy-phenyl)-propenone,
1-[2,4-Bis-(4-methyl-piperazin-1-yl)-phenyl]-3-(2,4-dichloro-phenyl)-propenone,
1-[2,4-Bis-(4-methyl-piperazin-1-yl)-phenyl]-3-(3-dimethylaminomethyl-phenyl)-propenone,
- 25 3-[3',5'-Dimethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-1-[2-(4-methyl-piperazin-1-yl)-phenyl]-propenone,
3-(2,4-Dichloro-phenyl)-1-[2-fluoro-6-(4-methyl-piperazin-1-yl)-phenyl]-propenone,
1-[2,4-Bis-(4-methyl-piperazin-1-yl)-phenyl]-3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
- 30 3-(3-Dimethylaminomethyl-phenyl)-1-[2-fluoro-6-(4-methyl-piperazin-1-yl)-phenyl]-propenone,
1-[2-Fluoro-6-(4-methyl-piperazin-1-yl)-phenyl]-3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
3-[5-Bromo-2-(4-methyl-piperazin-1-yl)-phenyl]-1-[2-(4-methyl-piperazin-1-yl)-phenyl]-
- 35 propenone,
3-(5-tert-Butyl-2-methoxy-phenyl)-1-[2-(4-methyl-piperazin-1-yl)-phenyl]-propenone,
3-(3-Dibutylamino-phenyl)-1-[2-(4-methyl-piperazin-1-yl)-phenyl]-propenone,
3-(2,4-Dichloro-phenyl)-1-[2-(4-methyl-piperazin-1-yl)-phenyl]-propenone,
3-(3-Dimethylaminomethyl-phenyl)-1-[2-(4-methyl-piperazin-1-yl)-phenyl]-propenone,
- 40 3-[2'-Methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-1-[2-(4-methyl-piperazin-1-yl)-phenyl]-propenone,
3-(5-tert-Butyl-2-methoxy-phenyl)-1-[4-hydroxy-2-(4-methyl-piperazin-1-yl)-phenyl]-propenone,

- 3-(3,5-Di-tert-butyl-2-methoxy-phenyl)-1-[4-hydroxy-2-(4-methyl-piperazin-1-yl)-phenyl]-propenone,
1-(3-Fluoro-4-hydroxy-phenyl)-3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
5 1-(3-Dimethylaminomethyl-4-hydroxy-phenyl)-3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
2-Dimethylamino-N-(3-{3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-acryloyl}-phenyl)-acetamide,
1-(2,6-Difluoro-phenyl)-3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-
10 propenone,
1-(3-Fluoro-4-methoxy-phenyl)-3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
1-(2-Fluoro-4-methoxy-phenyl)-3-[4'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
15 1-(2-Fluoro-4-methoxy-phenyl)-3-[3'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
3-[3',5'-Dimethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-1-(2-fluoro-4-methoxy-phenyl)-propenone,
1-(2-Fluoro-4-methoxy-phenyl)-3-[2-(4-methyl-piperazin-1-yl)-5-pyridin-3-yl-phenyl]-
20 propenone,
1-(4-Hydroxy-phenyl)-3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
N-(2-{3-[2'-Methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-acryloyl}-phenyl)-benzenesulfonamide,
25 1-(2-Fluoro-4-hydroxy-phenyl)-3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
N-[3'-(3-(2-Fluoro-4-methoxy-phenyl)-3-oxo-propenyl)-4'-(4-methyl-piperazin-1-yl)-biphenyl-4-yl]-acetamide,
3'-[3-(2-Fluoro-4-methoxy-phenyl)-3-oxo-propenyl]-4'-(4-methyl-piperazin-1-yl)-
30 biphenyl-4-carboxylic acid,
3-[4'-Amino-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-1-(2-fluoro-4-methoxy-phenyl)-propenone,
1-(2-Fluoro-4-methoxy-phenyl)-3-[4'-methanesulfonyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
35 1-(2-Fluoro-4-methoxy-phenyl)-3-[3'-hydroxymethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
1-(2-Fluoro-4-methoxy-phenyl)-3-[2-(4-methyl-piperazin-1-yl)-5-thiophen-3-yl-phenyl]-propenone,
1-(2-Fluoro-4-methoxy-phenyl)-3-[4'-hydroxymethyl-4-(4-methyl-piperazin-1-yl)-
40 biphenyl-3-yl]-propenone,
1-(2-Fluoro-4-methoxy-phenyl)-3-[4-(4-methyl-piperazin-1-yl)-4'-trifluoromethyl-biphenyl-3-yl]-propenone,
1-(2-Fluoro-4-methoxy-phenyl)-3-[2'-fluoro-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,

- 1-(2-Fluoro-4-methoxy-phenyl)-3-[4-(4-methyl-piperazin-1-yl)-3'-trifluoromethyl-biphenyl-3-yl]-propenone,
1-(2-Fluoro-4-methoxy-phenyl)-3-[4'-fluoro-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
5 1-(2-Fluoro-4-methoxy-phenyl)-3-[3'-fluoro-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
3-[5-Bromo-2-(4-methyl-piperazin-1-yl)-phenyl]-1-(2-fluoro-4-methoxy-phenyl)-propenone,
2-Dimethylamino-N-[3-(3-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-acryloyl)-phenyl]-acetamide,
10 3-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(3-dimethylaminomethyl-4-hydroxy-phenyl)-propenone,
3-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(4-hydroxy-phenyl)-propenone,
3-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(3-hydroxy-phenyl)-propenone,
15 3-[4-Bromo-2-(4-methyl-piperazin-1-yl)-phenyl]-1-(3-dimethylaminomethyl-4-hydroxy-phenyl)-propenone,
N-(3-{3-[4-Bromo-2-(4-methyl-piperazin-1-yl)-phenyl]-acryloyl}-phenyl)-2-dimethylamino-acetamide,
1-(2-Dimethylaminomethyl-phenyl)-3-[2'-methyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
20 1-(3-Dimethylaminomethyl-phenyl)-3-[2'-methyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
1-(3-Dimethylaminomethyl-4-hydroxy-phenyl)-3-[2'-methyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
25 1-(4-Hydroxy-phenyl)-3-[2'-methyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
1-(2-Fluoro-4-methoxy-phenyl)-3-[2'-methyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
2-Dimethylamino-N-(3-{3-[2'-methyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-acryloyl}-phenyl)-acetamide,
30 1-(3-Dimethylaminomethyl-4-methoxy-phenyl)-3-[2'-methyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
1-(2-Dimethylaminomethyl-phenyl)-3-[2'-methoxy-3-(4-methyl-[1,4]diazepan-1-yl)-biphenyl-4-yl]-propenone,
1-(3-Dimethylaminomethyl-phenyl)-3-[2'-methoxy-3-(4-methyl-[1,4]diazepan-1-yl)-biphenyl-4-yl]-propenone,
35 3-[2'-Methoxy-3-(4-methyl-piperazin-1-yl)-biphenyl-4-yl]-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
1-(2-{[(2-Dimethylamino-ethyl)-methyl-amino]-methyl}-phenyl)-3-[2'-methoxy-3-(4-methyl-piperazin-1-yl)-biphenyl-4-yl]-propenone,
40 1-{2-[(tert-Butyl-methyl-amino)-methyl]-phenyl}-3-[2'-methoxy-3-(4-methyl-piperazin-1-yl)-biphenyl-4-yl]-propenone,
1-(2-Dimethylaminomethyl-phenyl)-3-[5-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,

and salts thereof.

While the above-mentioned group of compounds is intended to include all stereoisomers, including optical isomers, and mixtures thereof, as well as pure, partially enriched, or, where relevant, racemic forms, the embodiment in which the enone moiety has the *E*-configuration is generally preferred.

In another aspect the invention provides combinatorial libraries, mixtures and kits for screening compounds as defined above.

10

In one embodiment, a combinatorial library comprising at least two compounds of the general formula is provided. Such library may be in the form of an equimolar mixture, or in a mixture of any stoichiometry. Typical embodiments comprise at least two, such as at least 10, such as at least 100, such as at least 1000, such as at least 10000, such as at least 100000 compounds as defined above.

15

In another embodiment, combinatorial compound collections in the form of kits for screening for biologically or pharmacologically active compounds are provided. Such kits comprise at least two topologically distinct singular compounds of the general formula defined above. Typical kits comprise at least 10, such as at least 100, such as at least 1000, such as at least 10000, such as at least 100000 compounds as defined above. Kits are preferably provided in the form of solutions of the compounds in appropriate solvents.

20

Further provided are methods for screening for pharmacologically active compounds, especially bacteriostatic, bacteriocidal and antiparasitic agents, consisting of the steps of preparing a kit or library comprising at least two compounds of the general formula defined above, contacting said kit or library with a target molecule, such as a protein or nucleic acid, a target tissue, or a target organism, such as a bacterium or parasite, and detecting a biological or pharmacological response caused by at least one compound. Optionally, the steps may be repeated as appropriate to achieve deconvolution.

25

30

Definitions

In the present context, the term "bacteriostatic" is intended to describe an antimicrobial activity of a test compound, characterized by an inhibition of bacterial growth in the absence of a reduction of viable bacteria (bacterial kill) during incubation with the test compound, as evidenced in the killing curve determination by a stationary number of colony forming units (CFU) during incubation time.

35

In the present context, the term "bacteriocidal" is intended to describe an antimicrobial activity of a test compound, characterized by the reduction of viable bacteria (bacterial kill) during incubation with the test compound, as evidenced in the killing curve determination by a reduction of colony forming units (CFU) during incubation time.

40

In the present contest, the term "antiparasitic" is intended to describe the ability of a test compound to upon incubation in vitro with a culture of parasites, e.g. *Leishmania major* or *Plasmodium falciparum*, to inhibit metabolic labelling of the parasites by at least 50% compared to mock treated control cultures.

5

In the present context, the term "C₁₋₁₂-alkyl" is intended to mean a linear, cyclic or branched hydrocarbon group having 1 to 12 carbon atoms, such as methyl, ethyl, propyl, *iso*-propyl, cyclopropyl, butyl, *tert*-butyl, *iso*-butyl, cyclobutyl, pentyl, cyclopentyl, hexyl, cyclohexyl, etc. Analogously, the term "C₁₋₆-alkyl" is intended to mean a linear, cyclic or branched hydrocarbon group having 1 to 6 carbon atoms, such as methyl, ethyl, propyl, *iso*-propyl, pentyl, cyclopentyl, hexyl, cyclohexyl, and the term "C₁₋₄-alkyl" is intended to cover linear, cyclic or branched hydrocarbon groups having 1 to 4 carbon atoms, e.g. methyl, ethyl, propyl, *iso*-propyl, cyclopropyl, butyl, *iso*-butyl, *tert*-butyl, cyclobutyl.

15 Whenever the term "C₁₋₁₂-alkyl" is used herein, it should be understood that a particularly interesting embodiment thereof is "C₁₋₆-alkyl".

Similarly, the terms " C_{2-12} -alkenyl", " C_{4-12} -alkadienyl", and " C_{6-12} -alkatrienyl" are intended to cover linear, cyclic or branched hydrocarbon groups having 2 to 12, 4 to 12, and 6 to 12, carbon atoms, respectively, and comprising one, two, and three unsaturated bonds, respectively. Examples of alkenyl groups are vinyl, allyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, heptadecaenyl. Examples of alkadienyl groups are butadienyl, pentadienyl, hexadienyl, heptadienyl, heptadecadienyl. Examples of alkatrienyl groups are hexatrienyl, heptatrienyl, octatrienyl, and heptadecatrienyl. Preferred examples of alkenyl are vinyl, allyl, butenyl, especially allyl.

Similarly, the term "C₂₋₁₂-alkynyl" is intended to mean a linear or branched hydrocarbon group having 2 to 12 carbon atoms and comprising a triple bond. Examples hereof are ethynyl, propynyl, butynyl, octynyl, and dodecaynyl.

30

Whenever the terms "C₂₋₁₂-alkenyl", "C₄₋₁₂-alkadienyl", "C₆₋₁₂-alkatrienyl", and "C₂₋₁₂-alkynyl" are used herein, it should be understood that a particularly interesting embodiment thereof are the variants having up to six carbon atoms.

35 In the present context, i.e. in connection with the terms "alkyl", "alkenyl", "alkadienyl",
"alkatrienyl", and "alkynyl", the term "optionally substituted" is intended to mean that the
group in question may be substituted one or several times, preferably 1-3 times, with
group(s) selected from hydroxy (which when bound to an unsaturated carbon atom may
be present in the tautomeric keto form), C₁₋₆-alkoxy (i.e. C₁₋₆-alkyl-oxy), C₂₋₆-alkenyloxy,
40 carboxy, oxo (forming a keto or aldehyde functionality), C₁₋₆-alkoxycarbonyl, C₁₋₆-
alkylcarbonyl, formyl, aryl, aryloxycarbonyl, aryloxy, arylamino, arylcarbonyl, heteroaryl,
heteroarylamino, heteroaryloxycarbonyl, heteroaryloxy, heteroarylcarbonyl, amino, mono-
and di(C₁₋₆-alkyl)amino, carbamoyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-
alkyl-aminocarbonyl, mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-aminocarbonyl, C₁₋₆-alkyl-

- carbonylamino, cyano, guanidino, carbamido, C₁₋₆-alkyl-sulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, C₁₋₆-alkanoyloxy, C₁₋₆-alkyl-sulphonyl, C₁₋₆-alkyl-sulphinyl, C₁₋₆-alkylsulphonyloxy, nitro, C₁₋₆-alkylthio, halogen, where any aryl and heteroaryl may be substituted as specifically describe below for "optionally substituted aryl and heteroaryl", and any alkyl, alkoxy, and the like representing substituents may be substituted with hydroxy, C₁₋₆-alkoxy, C₂₋₆-alkenyloxy, amino, mono- and di(C₁₋₆-alkyl)amino, carboxy, C₁₋₆-alkylcarbonylamino, halogen, C₁₋₆-alkylthio, C₁₋₆-alkyl-sulphonyl-amino, or guanidine.
- 10 Preferably, the substituents are selected from hydroxy (which when bound to an unsaturated carbon atom may be present in the tautomeric keto form), C₁₋₆-alkoxy (i.e. C₁₋₆-alkyl-oxy), C₂₋₆-alkenyloxy, carboxy, oxo (forming a keto or aldehyde functionality), C₁₋₆-alkylcarbonyl, formyl, aryl, aryloxy, arylamino, arylcarbonyl, heteroaryl, heteroarylamino, heteroaryloxy, heteroarylcarbonyl, amino, mono- and di(C₁₋₆-alkyl)amino; carbamoyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-aminocarbonyl, C₁₋₆-alkylcarbonylamino, guanidino, carbamido, C₁₋₆-alkyl-sulphonyl-amino, C₁₋₆-alkyl-sulphonyl, C₁₋₆-alkyl-sulphinyl, C₁₋₆-alkylthio, halogen, where any aryl and heteroaryl may be substituted as specifically describe below for "optionally substituted aryl and heteroaryl".
- 20 Especially preferred examples are hydroxy, C₁₋₆-alkoxy, C₂₋₆-alkenyloxy, amino, mono- and di(C₁₋₆-alkyl)amino, carboxy, C₁₋₆-alkylcarbonylamino, halogen, C₁₋₆-alkylthio, C₁₋₆-alkyl-sulphonyl-amino, and guanidine.
- 25 The terms "optionally substituted C₁₋₁₂-alkoxy" and "optionally substituted C₁₋₆-alkoxy" are intended to mean that the alkoxy groups may be substituted one or several times, preferably 1-3 times, with group(s) selected from hydroxy (which when bound to an unsaturated carbon atom may be present in the tautomeric keto form), C₁₋₆-alkoxy (i.e. C₁₋₆-alkyl-oxy), C₂₋₆-alkenyloxy, carboxy, oxo (forming a keto or aldehyde functionality), C₁₋₆-alkoxycarbonyl, C₁₋₆-alkylcarbonyl, formyl, aryl, aryloxycarbonyl, aryloxy, arylcarbonyl, heteroaryl, heteroaryloxycarbonyl, heteroaryloxy, heteroarylcarbonyl, carbamoyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-aminocarbonyl, cyano, guanidino, carbamido, C₁₋₆-alkyl-sulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, C₁₋₆-alkanoyloxy, C₁₋₆-alkyl-sulphonyl, C₁₋₆-alkyl-sulphinyl, C₁₋₆-alkylsulphonyloxy, nitro, C₁₋₆-alkylthio, halogen, where any aryl and heteroaryl may be substituted as specifically describe below for "optionally substituted aryl and heteroaryl".
- 30 C₁₋₆-alkoxycarbonyl, C₁₋₆-alkylcarbonyl, formyl, aryl, aryloxycarbonyl, aryloxy, arylcarbonyl, heteroaryl, heteroaryloxycarbonyl, heteroaryloxy, heteroarylcarbonyl, carbamoyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-aminocarbonyl, cyano, guanidino, carbamido, C₁₋₆-alkyl-sulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, C₁₋₆-alkanoyloxy, C₁₋₆-alkyl-sulphonyl, C₁₋₆-alkyl-sulphinyl, C₁₋₆-alkylsulphonyloxy, nitro, C₁₋₆-alkylthio, halogen, where any aryl and heteroaryl may be substituted as specifically describe below for "optionally substituted aryl and heteroaryl".
- 35 C₁₋₆-alkyl-sulphonyl, C₁₋₆-alkyl-sulphinyl, C₁₋₆-alkylsulphonyloxy, nitro, C₁₋₆-alkylthio, halogen, where any aryl and heteroaryl may be substituted as specifically describe below for "optionally substituted aryl and heteroaryl".

- Especially preferred examples of "optionally substituted C₁₋₁₂-alkoxy" and "optionally substituted C₁₋₆-alkoxy" groups are unsubstituted such groups, and those carrying one or two substituents selected from hydroxy, C₁₋₆-alkyl, C₁₋₆-alkoxy, C₂₋₆-alkenyloxy, carboxy, halogen, or C₁₋₆-alkylthio.
- 40

"Halogen" includes fluoro, chloro, bromo, and iodo.

In the present context the term "aryl" is intended to mean a fully or partially aromatic carbocyclic ring or ring system, such as phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, anthracyl; phenanthracyl, pyrenyl, benzopyrenyl, fluorenyl and xanthenyl, among which
 5 phenyl is a preferred example.

The term "heteroaryl" is intended to mean a fully or partially aromatic carbocyclic ring or ring system where one or more of the carbon atoms have been replaced with heteroatoms, e.g. nitrogen (=N- or -NH-), sulphur, and/or oxygen atoms. Examples of such heteroaryl
 10 groups are oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, coumaryl, furyl, thienyl, quinolyl, benzothiazolyl, benzotriazolyl, benzodiazolyl, benzooxazolyl, phthalazinyl, phthalanyl, triazolyl, tetrazolyl, isoquinolyl, acridinyl, carbazolyl, dibenzazepinyl, indolyl, benzopyrazolyl, phenoxazonyl. Particularly interesting heteroaryl groups are oxazolyl,
 15 isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, furyl, thienyl, quinolyl, triazolyl, tetrazolyl, isoquinolyl, indolyl in particular pyrrolyl, imidazolyl, pyridinyl, pyrimidinyl, thienyl, quinolyl, tetrazolyl, and isoquinolyl.

20 The term "heterocyclyl" is intended to mean a non-aromatic carbocyclic ring or ring system where one or more of the carbon atoms have been replaced with heteroatoms, e.g. nitrogen (=N- or -NH-), sulphur, and/or oxygen atoms. Examples of such heterocyclyl groups are imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, aziridine, azirine,
 25 azetidine, pyrrolane, tropane, oxazinane (morpholine), azepine, dihydroazepine, tetrahydroazepine, and hexahydroazepine, oxazolane, oxazepane, oxazocane, thiazolane, thiazinane, thiazepane, thiazocane, oxazetane, diazetane, thiazetane, tetrahydrofuran, tetrahydropyran, oxepane, tetrahydrothiophene, tetrahydrothiopyrane, thiepane, dithiane, dithiepane, dioxane, dioxepane, oxathiane, oxathiepane. The most interesting examples
 30 are imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, azetidine, tropane, oxazinane (morpholine), oxazolane, oxazepane, thiazolane, thiazinane, and thiazepane, in particular imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, pyrrolidine, piperidine, azepane, oxazinane (morpholine), and thiazinane.

35

In the present context, i.e. in connection with the terms "aryl", "heteroaryl", and heterocyclyl, the term "optionally substituted" is intended to mean that the group in question may be substituted one or several times, preferably 1-5 times, in particular 1-3
 40 times) with group(s) selected from hydroxy (which when present in an enol system may be represented in the tautomeric keto form), C₁₋₆-alkyl, C₁₋₆-alkoxy, C₂₋₆-alkenyl, oxo (which may be represented in the tautomeric enol form), carboxy, C₁₋₆-alkoxycarbonyl, C₁₋₆-alkylcarbonyl, formyl, aryl, aryloxy, arylamino, aryloxycarbonyl, arylcarbonyl, heteroaryl, heteroarylamino, amino, mono- and di(C₁₋₆-alkyl)amino; carbamoyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, mono- and di(C₁₋₆-alkyl)-

- amino-C₁₋₆-alkyl-aminocarbonyl, C₁₋₆-alkylcarbonylamino, cyano, guanidino, carbamido, C₁₋₆-alkanoyloxy, C₁₋₆-alkyl-sulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, C₁₋₆-alkyl-suphonyl, C₁₋₆-alkyl-sulphinyl, C₁₋₆-alkylsulphonyloxy, nitro, sulphanyl, amino, amino-sulfonyl, mono- and di(C₁₋₆-alkyl)amino-sulfonyl, dihalogen-C₁₋₄-alkyl,
- 5 trihalogen-C₁₋₄-alkyl, halogen, where aryl and heteroaryl representing substituents may be substituted 1-3 times with C₁₋₄-alkyl, C₁₋₄-alkoxy, nitro, cyano, amino or halogen, and any alkyl, alkoxy, and the like representing substituents may be substituted with hydroxy, C₁₋₆-alkoxy, C₂₋₆-alkenyloxy, amino, mono- and di(C₁₋₆-alkyl)amino, carboxy, C₁₋₆-alkylcarbonylamino, halogen, C₁₋₆-alkylthio, C₁₋₆-alkyl-sulphonyl-amino, or guanidine.
- 10 Preferably, the substituents are selected from hydroxy, C₁₋₆-alkyl, C₁₋₆-alkoxy, oxo (which may be represented in the tautomeric enol form), carboxy, C₁₋₆-alkylcarbonyl, formyl, amino, mono- and di(C₁₋₆-alkyl)amino; carbamoyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, C₁₋₆-alkylcarbonylamino, guanidino, carbamido, C₁₋₆-alkyl-
- 15 sulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, C₁₋₆-alkyl-suphonyl, C₁₋₆-alkyl-sulphinyl, C₁₋₆-alkylsulphonyloxy, sulphanyl, amino, amino-sulfonyl, mono- and di(C₁₋₆-alkyl)amino-sulfonyl or halogen, where any alkyl, alkoxy and the like representing substituents may be substituted with hydroxy, C₁₋₆-alkoxy, C₂₋₆-alkenyloxy, amino, mono- and di(C₁₋₆-alkyl)amino, carboxy, C₁₋₆-alkylcarbonylamino, halogen, C₁₋₆-alkylthio, C₁₋₆-
- 20 alkyl-sulphonyl-amino, or guanidine. Especially preferred examples are C₁₋₆-alkyl, C₁₋₆-alkoxy, amino, mono- and di(C₁₋₆-alkyl)amino, sulphanyl, carboxy or halogen, where any alkyl, alkoxy and the like representing substituents may be substituted with hydroxy, C₁₋₆-alkoxy, C₂₋₆-alkenyloxy, amino, mono- and di(C₁₋₆-alkyl)amino, carboxy, C₁₋₆-alkylcarbonylamino, halogen, C₁₋₆-alkylthio, C₁₋₆-alkyl-sulphonyl-amino, or guanidine.
- 25 In the present context the term "nitrogen-containing heterocyclic ring" is intended to mean heterocyclic ring or ring system in which at least one nitrogen atom is present. Such a nitrogen is, with reference to the formula, carrying the substituents R₁ and R₂. The "nitrogen-containing heterocyclic ring" may further comprise additional heteroatoms, e.g.
- 30 nitrogen (=N- or -N-), sulphur, and/or oxygen atoms. Examples of such rings are aromatic rings such as pyridine, pyridazine, pyrimidine, pyrazine, triazine, thiophene, oxazole, isoxazole, thiazole, isothiazole, pyrrole, imidazole, pyrazole, tetrazole, quinoline, benzothiazole, benzotriazole, benzodiazole, benzoxazole, triazole, isoquinoline, indole, benzopyrazole, thiadiazole, and oxadiazole. The most interesting examples of aromatic
- 35 rings are pyridine, pyridazine, pyrimidine, pyrazine, thiophene, tetrazole, oxazole, isoxazole, thiazole, isothiazole, pyrrole, imidazole, pyrazole, quinoline, triazole, isoquinoline, and indole, in particular pyridine, thiophene, imidazole, quinoline, isoquinoline, indole, and tetrazole.
- 40 Other examples of such rings are non-aromatic rings such as imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, aziridine, azirine, azetidione, pyrroline, tropane, oxazinane (morpholine), azepine, dihydroazepine, tetrahydroazepine, and hexahydroazepine, oxazolane, oxazepane, oxazocane, thiazolane, thiazinane, thiazepane, thiazocane, oxazetane,

diazetane, and thiazetane. The most interesting examples of non-aromatic rings are imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, azetidine, tropane, oxazinane (morpholine), oxazolane, oxazepane, thiazolane, thiazinane, and thiazepane, in particular

5 imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, pyrrolidine, piperidine, azepane, oxazinane (morpholine), and thiazinane.

In the present context, i.e. in connection with the term "nitrogen-containing heterocyclic ring", the term "optionally substituted" is intended to mean that the group in question may

10 be substituted one or several times, preferably 1-5 times, in particular 1-3 times) with group(s) selected from the same substituents as defined above for "optionally substituted aryl".

As is evident from the formulae defined herein and the definitions associated therewith,

15 embodiment of compounds of the present invention are chiral. Moreover, the presence of certain cyclic fragments or multiple stereogenic atoms provides for the existence of diastereomeric forms of some of the compounds. The invention is intended to include all stereoisomers, including optical isomers, and mixtures thereof, as well as pure, partially enriched, or, where relevant, racemic forms.

20

Embodiments where V is -CH=CH- may comprise *E*- and *Z*-stereoisomers, or mixtures of such isomers, which may exist in a dynamic equilibrium in solution. The *E*-isomers are generally preferred.

25 It should furthermore be understood that the compounds defined herein include possible salts thereof, of which pharmaceutically acceptable salts are of course especially relevant for the therapeutic applications. Salts include acid addition salts and basic salts. Examples of acid addition salts are hydrochloride salts, fumarate, oxalate, etc. Examples of basic salts are salts where the (remaining) counter ion is selected from alkali metals, such as

30 sodium and potassium, alkaline earth metals, such as calcium salts, potassium salts, and ammonium ions ($^+N(R')_4$, where the R's independently designates optionally substituted C₁₋₆-alkyl, optionally substituted C₂₋₆-alkenyl, optionally substituted aryl, or optionally substituted heteroaryl). Pharmaceutically acceptable salts are, e.g., those described in Remington's - The Science and Practice of Pharmacy, 20th Ed. Alfonso R. Gennaro (Ed.),

35 Lippincott, Williams & Wilkins; ISBN: 0683306472, 2000, and in Encyclopedia of Pharmaceutical Technology. However, generally preferred salt forming agents for application in the present invention are organic dicarboxylic acids such as oxalic, fumaric, and maleic acid, and the like.

40

Thus, chalcones with diamino groups can be prepared in their salt-forms thereby making the compounds particularly useful for pharmaceutical formulations. The use of appropriate selected salt form can be used to control the dissolution rate in vivo. Furthermore, the

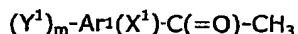
different salt forms have different bulk-properties which is of importance for the manufacturing process.

Preparation of compounds

- 5 The diamino-functional chalcones defined herein may be produced by methods known *per se* for the preparation of chalcones or methods which are analogous to such methods. Examples of excellent methods for preparing compounds of the 1,3-bis-aromatic-prop-2-enone or the 1,3-bis-aromatic-prop-2-ynone types are given in the following. Further examples of methods for the preparation of the compound used according to the present
10 invention are described in WO 95/06628 and WO 93/17671 and in the references cited therein.

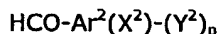
Compounds of the general formula I in which V is -CH=CH- can be prepared by reacting a ketone (an acetophenone in the case where Ar¹ is phenyl)

15



with an aldehyde (a benzaldehyde in the case where Ar² is phenyl)

20



wherein Ar¹, Ar², X¹, X², Y¹, Y², m, and p refer to the definitions given elsewhere herein.

- This reaction, which is a condensation reaction, is suitably carried out under acid or base
25 catalysed conditions. A review of such processes may be found in Nielsen, A.T., Houlihahn, W.J., *Org. React.* **16**, 1968, p 1-444. In particular the method described by Wattanasin, S. and Murphy, S., *Synthesis* (1980) 647 has been found quite successful. The reaction may suitably be carried out in protic organic solvents, such as lower alcohols (e.g. methanol, ethanol, or tert-butanol), or lower carboxylic acids (formic, glacial acetic, or propionic
30 acid), or in aprotic organic solvents such as ethers (e.g. tetrahydrofuran, dioxane, or diethyl ether), liquid amides (e.g. dimethylformamide or hexamethylphosphordiamide), dimethylsulfoxide, or hydrocarbons (e.g. toluene or benzene), or mixtures of such solvents. When carrying out the reaction under base catalysed conditions, the catalyst may be selected from sodium, lithium, potassium, barium, calcium, magnesium, aluminum,
35 ammonium, or quaternary ammonium hydroxides, lower alkoxides (e.g. methoxides, ethoxides, tert-butoxides), carbonates, borates, oxides, hydrides, or amides of lower secondary amines (e.g. diisopropyl amides or methylphenyl amides). Primary aromatic amines such as aniline, free secondary amines such as dimethyl amine, diethyl amine, piperidine, or pyrrolidine as well as basic ion exchange resins may also be used.

40

Acid catalysts may be selected from hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, sulfonic acids (such as paratoluenesulfonic or methanesulfonic acid), lower carboxylic acids (such as formic, acetic or propionic acid), lower halogenated

carboxylic acids (such as trifluoroacetic acid), Lewis acids (such as BF_3 , POCl_3 , PCl_5 , or FeCl_3), or acid ion exchange resins.

A drawback of the base catalysed condensation is the poor yield obtained if the aromatic ring in which the ketone or the aldehyde or both is substituted with one or more hydroxy groups. This drawback can be overcome by masking the phenolic group as described by T. Hidetsugu et al. in EP 0 370 461. Deprotection is easily performed by mineral acids such as hydrochloric acid.

10 The reaction is typically carried out at temperatures in the range of 0-100°C, e.g. at room temperature. Reaction times are typically from 30 min to 24 hours.

The starting materials for the synthesis (acetophenone and aldehyde), may be obtained from commercial sources or may be synthesised according to well-known methods. The diamino-benzaldehydes can be synthesized by Palladium catalysed reaction of bromo-benzaldehyde diethyl acetal and diamine followed by acidic work up. Alternatively, the 2-diamino-benzaldehydes can be prepared by nucleophilic aromatic substitution using 2-fluorobenzaldehyde and diamine. The diamino-acetophenones can be synthesized by Palladium catalysed reaction of bromoacetophenone ketal and diamine followed by acidic work up. Alternatively the 2'-diamino-acetophenones can be synthesized by nucleophilic aromatic substitution using 2'-fluoroacetophenone and diamine.

Compounds of the general formula I in which V is $-\text{C}\equiv\text{C}-$ may be prepared by reacting an activated derivative of a carboxylic acid of the general formula



with an ethyne derivative



wherein Ar^1 , Ar^2 , X^1 , X^2 , Y^1 , Y^2 , m , and p refer to the definitions given elsewhere herein.

Reactions of this type are described by Tohda, Y., Sonogashihara, K., Hagihara, N.,
35 *Synthesis* **1977**, p 777-778. It is contemplated that the activated derivative of the carboxylic acid may be an activated ester, an anhydride or, preferably, an acid halogenide, in particular the acid chloride. The reaction is normally carried out using the catalysts described by Tohda, Y. *et al.* cited above, namely copper(I)iodide/triphenylphosphine-palladium dichloride. The reaction is suitably carried out in triethylamine, a mixture of
40 triethylamine and pyridine or triethylamine and toluene under a dry inert atmosphere such as nitrogen or argon. The reaction is generally carried out at reduced temperature such as in the range from -80°C to room temperature, the reaction time typically being from 30 minutes to 6 hours.

In the above reactions, it may be preferred or necessary to protect various sensitive or reactive groups present in the starting materials to prevent said groups from interfering with the reactions. Such protection may be carried out in a well-known manner, e.g. as described in "Protective Groups in Organic Chemistry" by Wuts and Greene, Wiley-

- 5 Interscience; ISBN: 0471160199; 3rd edition (May 15, 1999). For example, in the reaction between the activated acid derivative and the acetylene derivative, a hydroxy group on Ar¹ and/or Ar² may be protected in the form of the methoxymethyl ether, N,N-dimethylcarbamoyl ester, or allyl ether. The protecting group may be removed after the reaction in a manner known *per se*.

10

The ethyne derivative may be prepared by standard methods, e.g. as described by Nielsen, S. F. Et al., Bloorg. Med. Chem. 6, pp 937-945 (1998). The carboxylic acids may likewise be prepared by standard procedures, e.g. as described by Nakayama, T. Chem. Pharm. Bull. 41, pp 117-125 (1993).

15

Compounds of the general formula I in which V is -CH₂-CH₂- can be prepared by ionic hydrogenation of the corresponding α,β -unsaturated compound where V is -CH=CH- as it has been described by the inventors in Nielsen, S.F. et al. Tetrahedron, 53, pp 5573-5580 (1997). Alternatively, it is possible to prepare such compounds from the corresponding
20 fluoro (or bromo) chalcones using H₂/Pt followed by nucleophilic aromatic amination (see Figure 3).

Further possible synthetic routes for the preparation of the saturated variants are described in "Advanced Organic Chemistry" by Jerry March, 3rd ed. (especially chapter 15,
25 pages 691-700) and references cited therein. Thus, it is possible to obtain a large variety of compounds of the 1,3-bis-aromatic-propan-1-one type from the corresponding prop-2-en-1-ones.

Therapeutic uses

- 30 The present inventors have found that that the novel compound have interesting properties as bacteriostatic, bacteriocidal and antiparasitic agents (see the Examples section). It is of course possible that the compounds also have other interesting properties to be utilised in the medical field.
- 35 Thus, the present invention provides, in a further aspect, a compound (chalcone derivative) as defined herein for use as a drug substance, i. e. a medicament.

- Moreover, in further aspects the invention relates to the use of the compounds as defined herein for the preparation of a medicament for the treatment of infections, such as
40 infections associated with bacteria, protozoas or *Leishmania spp*.

The invention also provides in still further aspects a method for the treatment of infections such as bacteria, protozoas or *Leishmania spp* in a mammal comprising the administration of the compounds as defined herein to said mammal.

In one aspect, the chalcone derivatives may be used for the treatment of bacterial infections in a mammal in need thereof. Such bacterial infection may be associated with common Gram-positive and/or Gram-negative pathogens or with microaerophilic or anaerobic bacteria. As a particularly relevant example of bacteria against which chalcone derivatives demonstrates an effect can be mentioned antibiotic-sensitive or -resistant strains of *S.aureus* and/or *E.faecium*. Other examples include community acquired and nosocomial respiratory infections, including *S.pneumoniae*, *S.pyogenes* and members of *Enterobacteriaceae* (e.g. *E.coli*), microaerophilic bacteria associated with gastric disease (e.g. *Helicobacter pylori*) or pathogenic anaerobic bacteria (e.g. *Bacteroides fragilis* and *Clostridium species*).

In this context, a preferred embodiment of the compound of the general formula above is the one wherein Ar^1 and Ar^2 are both phenyl, m is 0 or 1, p is 1, and V is $-CH=CH-$ or $-CH_2CH_2-$. Further preferred are such compounds where Y^2 is located in the 2-, 3- or 4-position, with the 2-position preferred, and optionally supplemented by additional groups as defined by X^1 , X^2 , and Y^1 . Suitable such compounds are those wherein X^2 is one substituent located in the 5-, or 6-position, and selected from optionally substituted phenyl, and those wherein X^1 is 0-3 substituents selected from amino, hydroxy, alkyl or arylsulfonamido, alkoxy, and halo and those wherein X^1 is 1-2 substituents selected from dialkylaminomethyl, hydroxy, and alkoxy. Typical locations of Y^1 , when present, are the 2-, 3- or 4-positions, with the 2- and 3-positions being preferred.

Another embodiment relevant for application in the context of bacterial infections is defined by Ar^1 and Ar^2 both being phenyl, m is 1, p is 0, and V is $-CH=CH-$ or $-CH_2CH_2-$. Preferred are such compounds where Y^1 is present one or two times. Further substitution as defined by X^1 and X^2 , each present 0-2 times, such as 0-1 time, also provides for suitable compounds. Typically, X^1 and X^2 , when present, are relatively large groups, preferably selected from the list comprising dialkylamino, optionally substituted phenyl, alkyl, alkenyl, alkoxy, and aryloxy.

In still another aspect the chalcone derivatives can be used for the treatment of infections caused by protozoa in a mammal. Examples of infections are those associated with protozoa selected from *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae*.

In this context, a preferred embodiment of the compound of the general formula above is the one wherein Ar^1 and Ar^2 are both phenyl, m is 1, p is 0 or 1, and V is $-CH=CH-$. Further preferred are such compounds where Y^1 is selected from 3- or 4-(2-(dimethylamino)ethyl)amino, 2- or 4-(2-(dimethylamino)ethyl)methylamino, 2- or 4-(3-(dimethylamino)propyl)amino, and 2-, 4- or 6-(4-methylpiperazin-1-yl). Even further preferred are such compounds wherein X^1 alkoxy, such as methoxy, halo, such as fluoro, or absent.

Among these preferred embodiments, X^2 may typically represent 2- and 4-substituents, suitably halo, such as chloro, or 2- and 5-substituents, suitably alkoxy, alkyl, or aryl, such as alkoxy, e. g. methoxy, combined with alkoxy, alkyl, or aryl, or a 3-substituent, typically dialkylamino or pyridinylamino, or 3- and 5-substituents, typically alkyl, such as trifluoromethyl, or a 4-substituent, such as imidazolyl, or even 2-, 4-, and 5-substituents, typically 2-alkoxy, 4-halo, and 5-alkyl, such as 2-methoxy, 4-chloro, and 5-alkyl. Further, in some of these preferred embodiments, Y^2 may typically represent a 2- or 3-(4-alkylpiperazin-1-yl) group, or a 2- or 4-(2-(dimethylamino)ethyl)methylamino group, especially in combination with additional substituents (X^2), such as alkyl, aryl, or halo groups, located in the 4-, 5-, or 6-position.

Another preferred embodiment, particularly relevant for treatment of infections caused by protozoa, of the compound of the general formula above is the one wherein Ar^1 and Ar^2 are both phenyl, m is 0, p is 1, and V is $-CH=CH-$. Further preferred are such compounds where Y^2 is selected from 2- or 3-(2-(dimethylamino)ethyl)amino, 2- or 3-(3-(dimethylamino)propyl)amino, 2- or 3-(piperazin-1-yl), 2- or 3-(4-alkylpiperazin-1-yl), 2- or 3-(4-acylpiperazin-1-yl), 2-(1,4-diazepan-1-yl), 2-(4-(alkylamino)piperidin-1-yl), and 2-(4-(pyrrolidin-1-yl)piperidin-1-yl). X^2 is typically 0-2 substituents selected from halogen and aryl, located in the 4-, 5-, or 6-positions.

In this preferred embodiment, X^1 suitably represents 0-3, such as 0-2, preferably 0-1 substituents, typically selected from the list comprising 2- or 3-dialkylaminomethyl, 2- or 3-heterocyclylmethyl, wherein the heterocyclyl ring contains at least one nitrogen, 2-, 3-, 4- or 6-alkoxy, 2-, 3-, 4- or 6-halo, 2-, 3-, 4- or 6-hydroxy, 2-(alkylsulfonamido), such as propylsulfonamido, and 2-(arylsulfonamido).

In a still further aspect, the chalcone derivatives as defined herein can be used for the treatment of infections in a mammal associated with *Leishmania spp.* Such infections may be cutaneous and/or visceral.

In this context, a preferred embodiment of the compound of the general formula above is the one wherein Ar^1 and Ar^2 are both phenyl, m is 1, p is 0 or 1, and V is $-CH=CH-$. Further preferred are such compounds where Y^1 is selected from (2-aminoethyl)amino, (2-alkylamino)ethylamino, (2-dialkylaminoethyl)amino, (3-aminopropyl)amino, (3-alkylamino)propylamino, and (3-dialkylaminopropyl)amino, each located in the 2-, 3- or 4-position, with the 3- or 4-position being preferred. Optionally, compounds in this embodiment may have additional substituents (X^2), such as halo or alkoxy groups, located at the 2-, 3- or 4-positions of Ar^2 .

Another preferred embodiment, particularly relevant for treatment of infections associated with *Leishmania*, of the compound of the general formula above is the one wherein Ar^1 and Ar^2 are both phenyl, m is 0, p is 1, and V is $-CH=CH-$. Especially suitable within this embodiment are compounds where Y^2 is 4-alkylpiperazin-1-yl, located in the 2-position, optionally supplemented by a 5-alkyl or 5-aryl substituent (X^2). In such embodiments, preferred meanings of X^1 include 2-, 3- and/or 4-alkyl, 2-, 3- and/or 4-alkoxy, 2-, 3- and/or 4-halo, and 2-, 3- and/or 4-(dialkylamino)methyl.

Formulation of pharmaceutical compositions

The chalcone derivatives are typically formulated in a pharmaceutical composition prior to use as a drug substance.

5

The administration route of the compounds (diamino-functional chalcones) as defined herein may be any suitable route which leads to a concentration in the blood or tissue corresponding to a therapeutic concentration. Thus, e.g., the following administration routes may be applicable although the invention is not limited thereto: the oral route, the
10 parenteral route, the cutaneous route, the nasal route, the rectal route, the vaginal route and the ocular route. It should be clear to a person skilled in the art that the administration route is dependant on the particular compound in question, particularly, the choice of administration route depends on the physico-chemical properties of the compound together with the age and weight of the patient and on the particular disease or
15 condition and the severity of the same.

The compounds as defined herein may be contained in any appropriate amount in a pharmaceutical composition, and are generally contained in an amount of about 1-95% by weight of the total weight of the composition. The composition may be presented in a
20 dosage form which is suitable for the oral, parenteral, rectal, cutaneous, nasal, vaginal and/or ocular administration route. Thus, the composition may be in form of, e.g., tablets, capsules, pills, powders, granulates, suspensions, emulsions, solutions, gels including hydrogels, pastes, ointments, creams, plasters, drenches, delivery devices, suppositories, enemas, injectables, implants, sprays, aerosols and in other suitable form.

25

The pharmaceutical compositions may be formulated according to conventional pharmaceutical practice, see, e.g., "Remington's Pharmaceutical Sciences" and "Encyclopedia of Pharmaceutical Technology", edited by Swarbrick, J. & J. C. Boylan, Marcel Dekker, Inc., New York, 1988. Typically, the compounds defined herein are
30 formulated with (at least) a pharmaceutically acceptable carrier or excipient. Pharmaceutically acceptable carriers or excipients are those known by the person skilled in the art.

Thus, the present invention provides a pharmaceutical composition comprising a
35 compound as defined herein in combination with a pharmaceutically acceptable carrier.

Pharmaceutical compositions according to the present invention may be formulated to release the active compound substantially immediately upon administration or at any substantially predetermined time or time period after administration. The latter type of
40 compositions are generally known as controlled release formulations.

In the present context, the term "controlled release formulation" embraces i) formulations which create a substantially constant concentration of the drug within the body over an extended period of time, ii) formulations which after a predetermined lag time create a

- substantially constant concentration of the drug within the body over an extended period of time, iii) formulations which sustain drug action during a predetermined time period by maintaining a relatively, constant, effective drug level in the body with concomitant minimization of undesirable side effects associated with fluctuations in the plasma level of the active drug substance (sawtooth kinetic pattern), iv) formulations which attempt to localize drug action by, e.g., spatial placement of a controlled release composition adjacent to or in the diseased tissue or organ, v) formulations which attempt to target drug action by using carriers or chemical derivatives to deliver the drug to a particular target cell type.
- 10 Controlled release formulations may also be denoted "sustained release", "prolonged release", "programmed release", "time release", "rate-controlled" and/or "targeted release" formulations.

- Controlled release pharmaceutical compositions may be presented in any suitable dosage forms, especially in dosage forms intended for oral, parenteral, cutaneous nasal, rectal, vaginal and/or ocular administration. Examples include single or multiple unit tablet or capsule compositions, oil solutions, suspensions, emulsions, microcapsules, microspheres, nanoparticles, liposomes, delivery devices such as those intended for oral, parenteral, cutaneous, nasal, vaginal or ocular use.

20

- Preparation of solid dosage forms for oral use, controlled release oral dosage forms, fluid liquid compositions, parenteral compositions, controlled release parenteral compositions, rectal compositions, nasal compositions, percutaneous and topical compositions, controlled release percutaneous and topical compositions, and compositions for administration to the eye can be performed essentially as described in the applicant's earlier International application No. WO 99/00114, page 29, line 9, to page 40, line 3. Also, and more generally, the formulation and preparation of the above-mentioned compositions are well-known to those skilled in the art of pharmaceutical formulation. Specific formulations can be found in "Remington's Pharmaceutical Sciences".

30

Dosages

The compound are preferably administered in an amount of about 0.1-50 mg per kg body weight per day, such as about 0.5-25 mg per kg body weight per day.

- 35 For compositions adapted for oral administration for systemic use, the dosage is normally 2 mg to 1 g per dose administered 1-4 times daily for 1 week to 12 months depending on the disease to be treated.

- The dosage for oral administration for the treatment of parasitic diseases is normally 1 mg to 1 g per dose administered 1-2 times daily for 1-4 weeks, in particular the treatment of malaria is to be continued for 1-2 weeks whereas the treatment of leishmaniasis will normally be carried out for 3-4 weeks.

40

The dosage for oral administration for the treatment of bacterial diseases is normally 1 mg to 1 g per dose administered 1-4 times daily for 1 week to 12 months; in particular, the treatment of tuberculosis will normally be carried out for 6-12 months.

- 5 The dosage for oral administration of the composition in order to prevent diseases is normally 1 mg to 75 mg per kg body weight per day. The dosage may be administered once or twice daily for a period starting 1 week before the exposure to the disease until 4 weeks after the exposure.
- 10 For compositions adapted for rectal use for preventing diseases, a somewhat higher amount of the compound is usually preferred, i.e. from approximately 1 mg to 100 mg per kg body weight per day.

- For parenteral administration, a dose of about 0.1 mg to about 50 mg per kg body weight per day is convenient. For intravenous administration a dose of about 0.1 mg to about 20 mg per kg body weight per day administered for 1 day to 3 months is convenient. For intraarticular administration a dose of about 0.1 mg to about 20 mg per kg body weight per day is usually preferable. For parenteral administration in general, a solution in an aqueous medium of 0.5-2% or more of the active ingredients may be employed.

20

For topical administration on the skin, a dose of about 1 mg to about 5 g administered 1-10 times daily for 1 week to 12 months is usually preferable.

- In many cases, it will be preferred to administer the compound defined herein together with another antiparasitic, antimycotic or antibiotic drug, thereby reducing the risk of development of resistance against the conventional drugs, and reducing the amount of each of the drugs to be administered, thus reducing the risk of side effects caused by the conventional drugs. Important aspects of this is the use of the compound against Leishmania, where the compound I is combined with another antileishmanial drug, or the antimalarial use of the compound I where the compound I is used together with another antimalarial drug.

30

Method of prediction

- 35 In a separate aspect, the present invention also provides a method of predicting whether a chemical compound has a potential inhibitory effect against a microorganism selected from *Helicobacter pylori* and *Plasmodium falciparum*, said method comprising preparing a mixture of a dihydroorotate dehydrogenase, a substrate for dihydroorotate dehydrogenase and the chemical compound, measuring the enzymatic activity of dihydroorotate dehydrogenase (A), comparing the enzymatic activity of dihydroorotate dehydrogenase (A) with the standard activity of dihydroorotate dehydrogenase (B) corresponding to the activity of a dihydroorotate dehydrogenase in a similar sample, but without the chemical compound, predicting that the chemical compound has a potential inhibitory effect against *Helicobacter pylori* and *Plasmodium falciparum* if A is significantly lower than B.

40

The method can be performed as described under *DHODH Assay* in the Examples section. It should be noted that the method is not only applicable for the chalcone derivatives defined herein, but can be generally applied to predict the potential inhibitory effect of any compound. Preferably, however, the chemical compound is a chalcone derivative, e.g. a chalcone derivative as defined herein.

EXAMPLES

Preparation of compounds

Chemical names presented below were generated using the software ChemDraw Ultra, version 6.0.1, from CambridgeSoft.com.

The general method for the preparation of the A ring or B ring having the diamino-functional group is illustrated in Figure 1.

15 General procedure A

Amination of bromobenzaldehydes

Bromobenzaldehyde diethyl acetal (40 mmol), amine (48 mmol), $\text{Pd}_2(\text{dba})_3$ (0.2 mmol, 1 mol% Pd), *rac*-BINAP (0.6 mmol) and Na-*t*-OBu (68 mmol) was stirred in degassed toluene (60 mL) at 80°C for 18 h. The darkbrown mixture was poured into icecold hydrochloric acid (1 M, 200 mL) and stirred vigorously for 2 hours at 25°C. The solution was cooled to 0°C and pH was adjusted to 13 using 6M NaOH(aq) and extracted with Et_2O (4 x 100 mL). The organic phase was dried (K_2CO_3) and the solvent was removed under reduced pressure. The resulting crude oil purified by flash chromatography using 5% Et_3N in EtOAc.

25

General procedure B

Nucleophilic aromatic substitution on Fluorobenzaldehyde

A stirred solution of fluoro-benzaldehyde (49.3 mmol) in dry DMF (50 mL) was added K_2CO_3 (10.2 g, 74.0 mmol) and amine (74 mmol) and left overnight at 100°C. The reaction mixture was cooled to room temperature, added water (100 mL) and extracted with ether (3 x 50 mL). The combined organic phases was washed with water and dried (Na_2SO_4). Evaporation *in vacuo* and recrystallization (heptane) gave the product.

General Procedure C

35 Amination of bromoacetophenones

3'- or 4'-bromoacetophenone was converted into the corresponding cyclic ketal. A solution of 3- or 4-bromoacetophenone (0.10 mol), 1,3-propandiol (0.12 mol) and p-TsOH (0.1 g) in toluene (200 mL) was heated and water was azeotropically removed using a Dean-Stark water-separator. After 18 hours, the solution was washed with 5% Na_2CO_3 (100 ml), dried (K_2CO_3) and the solvent was removed under reduced pressure. According to ^1H NMR the ketals was pure enough for further reaction.

3'- or 4'-bromoacetophenone ketal (40 mmol), amine (48 mmol), Pd₂(dba)₃ (0.2 mmol, 1 mol% Pd), *rac*-BINAP (0.6 mmol) and Na-*t*-OBu (68 mmol) was stirred in degassed toluene (60 mL) at 80°C for 18 h. The darkbrown mixture was poured into icecold hydrochloric acid (1 M, 200 mL) and stirred vigorously for 2 hours at 25°C. The solution
5 was cooled to 0°C and pH was adjusted to 13 using 6M NaOH(aq) and extracted with Et₂O (4 x 100 mL). The organic phase was dried (K₂CO₃) and the solvent was removed under reduced pressure. The resulting crude oil purified by flash chromatography using 5% Et₃N in EtOAc.

10 General procedure D.

Nucleophilic aromatic substitution on Fluoroacetophenone

A mixture of Fluoroacetophenone (40 mmol), amine (50 mmol), K₂CO₃ (50 mmol) was refluxed in dry DMF (20 mL) under an argon atmosphere for 18 h. The DMF was removed using an oilpump and water (50 mL) was added to the residue. The water phase was
15 extracted with Et₂O (2 x 100 mL) and the organic phase was dried (K₂CO₃) and evaporated to yellow oil, which was pure enough for further reaction.

General procedure E

Preparation of alkyl aminomethyl acetophenones

20 To a solution of (2-methyl-[1,3]dioxan-2-yl) benzaldehyde (165 mmol) and amine (247 mmol) in dry THF (1.5 L) was added sodium triacetoxymethylborohydride (257mmol) under argon. The resulting suspension was stirred at room temperature for 18 hr. A solution of sodium hydroxide (2M) was added and stirring was continued for approximately 30 min, before the mixture was acidified using HCl (6M). The mixture was stirred for 1 hr. and
25 extracted with diethyl ether, which was discarded. The pH of the aqueous phase was adjusted to 11 – 14 using sodium hydroxide and extracted again with diethyl ether. The latter organic phase, was dried over sodium sulphate, filtered and evaporated to give the title products, which were used without further purification.

30 General procedure F

Preparation of alkyl aminomethyl benzaldehydes

To a solution of diethoxymethyl benzaldehyde (16.5 mmol) and amine (24.7 mmol) in dry THF (150 mL) was added sodium triacetoxymethylborohydride (25.7mmol) under argon. The resulting suspension was stirred at room temperature for 6-18 hr. A solution of sodium
35 hydroxide (2M) was added and stirring was continued for approximately 30 min, before the mixture was acidified using HCl (6M). The mixture was stirred for 1 hr. and extracted with diethyl ether, which was discarded. The pH of the aqueous phase was adjusted to 11 – 14 using sodium hydroxide and extracted again with diethyl ether. The latter organic phase, was dried over sodium sulphate, filtered and evaporated to give the title products, which
40 were used without further purification.

General procedure G

Preparation of biaryl carbaldehydes

A solution of Na_2CO_3 (44 mmol) in water (20 mL) was added to a solution of bromobenzaldehyde (14.7 mmol) and (hetero)arylboronic acid (17.6 mmol) in DME (40 mL). The mixture was flushed with argon for 2 minutes followed by addition of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (310 mg, 3 mol %). The reaction was heated at reflux and left overnight under an atmosphere of argon. The reaction was cooled, 2M Na_2CO_3 was added, and the mixture was extracted with EtOAc (3 x 20 mL). The title products were purified by flash chromatography.

General Procedure H

10 Amino-acylation of amino-acetophenones and amino-benzaldehydes.

A solution of amino-acetophenone/benzaldehyde (25 mmol) in THF (100 mL) was added chloroacetyl chloride (30 mmol). The mixture was stirred for 30 min, poured into icecold 2M NaOH (aq) and extracted with Et_2O . The organic phase was dried and the solvent was removed under reduced pressure giving the pure product. A solution of the product (10 mmol) and triethyl amine (30 mmol) in ethanol was added amine (20 mmol) and the mixture was refluxed for 4 hours. Ethanol was removed under reduced pressure and the product was dissolved in EtOAc and washed with 2M NaOH (aq). EtOAc was removed under reduced pressure giving the product as a pure oil.

20 General Procedure I

Synthesis of (amino-)chalcones

To a solution of an acetophenone (2 mmol) and a benzaldehyde (2 mmol) in 96% EtOH (10 mL) was added 8M NaOH (0.3 mL), and the mixture was stirred for 3-18 hours at 25°C. The mixture was evaporated on Celite® and the product was isolated by flash chromatography. The aminochalcone was dissolved in MeOH: Et_2O (1:9 v/v, 10 mL) and a solution of fumaric acid or oxalic acid in MeOH: Et_2O (1:9 v/v) was added. The salt was filtered off and recrystallised from MeOH or MeCN. Some aminochalcones did not undergo saltformation, and was isolated as the free base. The purity was >95% determined by HPLC and the molecular weight was determined by LC-MS.

30

General Procedure J

Synthesis of (hetero)aryl chalcones from bromo-chalcones

A solution of bromo-chalcone (0.92 mmol) and (hetero)aryl boronic acid (1.11 mmol) in DME (10 mL) was added a solution of Na_2CO_3 (290 mg, 2.8 mmol) in water (5 mL). The mixture was bubbled through with argon for 2 minutes followed by addition of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (19 mg, 3 mol %). The reaction was heated to reflux and left overnight under an atmosphere of argon. The solution was cooled, added 2M Na_2CO_3 , extracted with ether (3 x 20 mL) and purified by column chromatography.

40 General Procedure K

Synthesis of fluoro-(or bromo-)dihydrochalcones.

Fluoro- (or bromo-)chalcone was dissolved in EtOAc (100 mL), and 5% Pt/C (100 mg) was added and the mixture was hydrogenated at 1 bar H_2 . The addition of hydrogen was stopped when the theoretical amount was absorbed (1 eqv. H_2). The mixture was filtered

and evaporated leaving the product as an oil. The product was purified by column chromatography or crystallisation.

General Procedure L

- 5 Synthesis of fluoro- (or bromo)-diamino-dihydrochalcones
A mixture of fluoro-dihydrochalcone (4.5 mmol), amine (6.0 mmol), K_2CO_3 (0.83 g, 6.0 mmol) was refluxed in dry degassed DMF (6 mL) for 24 h. The red mixture was poured into water (100 mL) and extracted with EtOAc (3 x 30 mL), dried (K_2CO_3) and the solvent was removed under reduced pressure. The resulting dark oil was purified by column
10 chromatography (SiO_2) using EtOAc as eluent.

General Procedure M

Acylation of amines

- A solution of an amine (4 mmol) and triethyl amine (8 mmol) in diethyl ether (40 ml) was
15 added acyl chloride (4.8 mmol). The mixture was stirred for 30 min and the extracted with water. Diethyl ether was removed under reduced pressure giving the desired product as an oil.

Characterisation of the compounds

- 20 The compounds were characterised by NMR (300 MHz) and GC-MS/LC-MS

2-(5-Bromo-2-methoxy-phenyl)-[1,3]dioxane:

- A solution of 5-bromo-*o*-anisaldehyde (25 g, 116 mmol), 1,3-propandiol (9 mL, 125 mmol), *p*-toluenesulphonic acid (0.1 g) in toluene (150 mL) was heated and water was
25 azeotropically removed using a Dean-Stark water-separator. After 18 hours, the solution was washed with 5% Na_2CO_3 (100 ml), dried (K_2CO_3) and the solvent was removed under reduced pressure. The acetal was purified by vacuum distillation and isolated as clear oil:
bp: 126-130°C/0.05 mbar.

- 1H -NMR ($CDCl_3$): δ 7.74 (d, 1H), 7.38 (dd, 1H), 6.75 (d, 1H), 5.82 (s, 1H), 4.28-4.20 (m,
30 2H), 4.04-3.92 (m, 2H), 3.80 (s, 3H), 2.33-2.13 (m, 1H), 1.48-1.38 (m, 1H).

5-Dibutylamino-2-methoxy-benzaldehyde:

- 2-(5-Bromo-2-methoxy-phenyl)-[1,3]dioxane (40 mmol), di-*n*-butylamine (48 mmol), $Pd_2(dba)_3$ (0.2 mmol, 1 mol% Pd), $P(o\text{-tol})_3$ (0.6 mmol) and Na-*t*-OBu (68 mmol) was
35 stirred in degassed toluene (60 mL) at 80°C for 18 h. The darkbrown mixture was poured into icecold hydrochloric acid (1 M, 200 mL) and stirred vigorously for 2 hours at 25°C. The solution was cooled to 0°C and pH was adjusted to 9 using 6M NaOH(aq) and extracted with Et_2O (4 x 100 mL). The organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The resulting crude oil purified by flash chromatography
40 using EtOAc/*n*-heptane (1:4, v/v) as eluent. The product was isolated as yellow oil in 46% yield.

- 1H -NMR ($CDCl_3$): δ 9.98 (s, 1H), 7.15 (d, 1H), 6.92 (d, 1H), 6.79 (dd, 1H), 3.80 (s, 3H),
3.25 (t, 4H), 1.55-1.40 (m, 4H), 1.40-1.25 (m, 4H), 0.91 (t, 6H).

2-[(2-Dimethylamino-ethyl)-methyl-amino]benzaldehyde

General procedure B gave the title compound as yellow oil in 56% yield. ref.1

¹H-NMR (CDCl₃): δ 10.29 (s, 1H), 7.82-7.75 (dd, 1H), 7.53-7.43 (td, 1H), 7.13 (d, 1H), 7.05 (t, 1H), 3.25 (t, 2H), 2.92 (s, 3H), 2.52 (t, 2H), 2.22 (s, 6H).

5

3-(2-Dimethylamino-ethylamino)benzaldehyde

General procedure A gave the title compound as yellow oil in 52% yield.

¹H-NMR (CDCl₃): δ 9.81 (s, 1H), 7.65 (d, 2H), 6.60 (d, 2H), 5.11 (s, br, 1H), 3.20-3.14 (m, 2H), 2.56 (t, 2H), 2.26 (s, 6H).

10

3-[(2-Dimethylamino-ethyl)-methyl-amino]benzaldehyde

General procedure A gave the title compound as yellow oil in 90% yield.

¹H-NMR (CDCl₃): δ 9.91 (s, 1H), 7.35 (t, 1H), 7.12-7.05 (m, 2H), 7.00-6.93 (dd, 1H), 3.56 (t, 2H), 3.05 (s, 3H), 2.55 (t, 2H), 2.38 (s, 6H).

15

4-[(2-Dimethylamino-ethyl)-methyl-amino]benzaldehyde

General procedure A gave the title compound as yellow oil in 66% yield ref. 2

¹H-NMR (CDCl₃): δ 9.73 (s, 1H), 7.73 (d, 2H), 6.71 (d, 2H), 3.54 (t, 2H), 3.08 (s, 3H), 2.50 (t, 2H), 2.30 (s, 6H).

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3-(Pyridin-3-ylamino)-benzaldehyde

General procedure A gave the title compound as white crystal in 69% yield.

¹H-NMR (DMSO-d₆): δ 9.94 (s, 1H), 8.67 (s, 1H), 8.40 (d, 1H), 8.11 (dd, 1H), 7.58-7.50 (m, 2H), 7.47 (d, 1H), 7.43-7.35 (m, 2H), 7.29 (dd, 1H).

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4-(2-Dimethylamino-ethylamino) benzaldehyde

General procedure A gave the title compound as a yellow oil in 74% yield ref. 2

¹H-NMR (CDCl₃): δ 9.71 (s, 1H), 7.68 (d, 2H), 6.61 (d, 2H), 5.08 (s, br, 1H), 3.24-3.18 (m, 2H), 2.57 (t, 2H), 2.26 (s, 6H).

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5-Bromo-2-(4-methyl-piperazin-1-yl)-benzaldehyde

General procedure B gave the title compound as yellow crystals in 62% yield.

¹H NMR (CDCl₃) δ 10.24 (s, 1H), 7.91 (d, 1H), 7.61 (dd, 1H), 7.02 (d, 1H), 3.11 (t, 4H), 2.63 (t, 4H), 2.39 (s, 3H).

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2-Bromo-5-(4-methyl-piperazin-1-yl)-benzaldehyde

A solution of 3-(4-Methyl-piperazin-1-yl)-benzaldehyde (49 mmol) in methylene chloride (150 ml) was slowly (30 min) added a solution of N-bromosuccinimide (98 mmol) in methylene chloride (450 ml). The mixture was stirred for 10 min, washed with 2M sodium hydroxide and the organic phase was removed under reduced pressure. The resulting oil was purified by column chromatography giving the title compound as 90% pure black oil in 95% yield (the impurity being 4-bromo-3-(4-methyl-piperazin-1-yl)-benzaldehyde).

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¹H NMR (CDCl₃): δ 10.29 (s, 1H), 7.47 (d, 1H), 7.40 (d, 1H), 7.00 (dd, 1H), 3.26 (t, 4H), 2.58 (t, 4H), 2.36 (s, 3H).

4-[(2-Dimethylamino-ethyl)-methyl-amino]-3',5'-dimethyl-biphenyl-3-carbaldehyde

General procedure B gave the title compound as yellow oil in 72% yield.

- 5 ¹H NMR (DMSO-d₆): δ 10.19 (s, 1H), 7.89 (d, 1H), 7.81 (dd, 1H), 7.27-7.25 (m, 3H), 6.97 (bs, 1H), 3.25 (t, 2H), 2.92 (s, 3H), 2.47 (t, 2H), 2.33 (s, 6H), 2.12 (s, 6H).

4-(3-Formyl-3',5'-dimethyl-biphenyl-4-yl)-piperazine-1-carboxylic acid tert-butyl ester

- 10 General procedure B gave the title compound as semi-solid in 100% yield.

¹H NMR (DMSO-d₆): δ 10.28 (s, 1H), 7.95 (d, 1H), 7.89 (dd, 1H), 7.30-7.27 (m, 3H), 6.99 (bs, 1H), 3.54 (t, 4H), 3.04 (t, 4H), 2.33 (s, 6H), 1.43 (s, 9H).

3-Fluoro-2'-methyl-biphenyl-4-carbaldehyde

- 15 General Procedure G gave the title compound as yellow oil in 80% yield.

¹H NMR (DMSO-d₆): δ 10.26 (s, 1H), 7.90 (t, 1H), 7.45-7.25 (m, 6H), 2.26 (s, 3H).

3-[(2-Dimethylamino-ethyl)-methyl-amino]-2'-methyl-biphenyl-4-carbaldehyde

General procedure B gave the title compound as brown oil in 82% yield.

- 20 ¹H NMR (DMSO-d₆): δ 10.19 (s, 1H), 7.71 (d, 1H), 7.32-7.23 (m, 4H), 7.09 (d, 1H), 7.00 (dd, 1H), 3.25 (t, 2H), 2.90 (s, 3H), 2.47 (t, 2H), 2.25 (s, 3H), 2.10 (s, 6H).

3-(4-Methyl-piperazin-1-yl)-benzaldehyde

General procedure A gave the title compound as brown oil in 77% yield.

- 25 ¹H NMR (DMSO-d₆): δ 9.94 (s, 1H), 7.45-7.40 (m, 2H), 7.31-7.27 (m, 2H), 3.21 (t, 4H), 2.46 (t, 4H), 2.22 (s, 3H).

4-(4-Methyl-piperazin-1-yl)-biphenyl-2-carbaldehyde

General Procedure G gave the title compound as yellow crystals in 35% yield.

- 30 ¹H NMR (DMSO-d₆): δ 9.85 (s, 1H), 7.51-7.36 (m, 8H), 3.25 (t, 4H), 2.47 (t, 4H), 2.23 (s, 3H).

2'-Methyl-4-(4-methyl-piperazin-1-yl)-biphenyl-2-carbaldehyde

General Procedure G gave the title compound as yellow crystals in 38% yield.

- 35 ¹H NMR (DMSO-d₆): δ 9.61 (s, 1H), 7.66-7.53 (m, 1H), 7.38-7.14 (m, 6H), 3.25 (t, 4H), 2.48 (t, 4H), 2.24 (s, 3H), 2.05 (s, 3H).

3-Bromo-5-(4-methyl-piperazin-1-yl)-benzaldehyde

General procedure A gave the title compound as yellow oil in 29% yield.

- 40 ¹H NMR (DMSO-d₆): δ 9.89 (s, 1H), 7.44-7.37 (m, 3H), 3.25 (t, 4H), 2.44 (t, 4H), 2.22 (s, 3H).

5-(4-Methyl-piperazin-1-yl)-biphenyl-3-carbaldehyde

General Procedure G gave the title compound as yellow crystals in 44% yield.

¹H NMR (DMSO-d₆): δ 10.01 (s, 1H), 7.75-7.72 (m, 2H), 7.58 (t, 1H), 7.51-7.40 (m, 5H), 3.31 (t, 4H), 2.49 (t, 4H), 2.24 (s, 3H).

2'-Methyl-5-(4-methyl-piperazin-1-yl)-biphenyl-3-carbaldehyde

- 5 General Procedure G gave the title compound as yellow oil in 74% yield.

¹H NMR (DMSO-d₆): δ 9.98 (s, 1H), 7.41 (m, 1H), 7.32-7.22 (m, 5H), 7.18 (m, 1H), 3.25 (t, 4H), 2.48 (t, 4H), 2.24 (s, 3H), 2.22 (s, 3H).

3-Bromo-5-[(2-dimethylamino-ethyl)-methyl-amino]-benzaldehyde

- 10 General procedure A gave the title compound as yellow oil in 56% yield.

¹H NMR (DMSO-d₆): δ 9.87 (s, 1H), 7.21 (t, 1H), 7.17-7.16 (m, 1H), 7.07 (t, 1H), 3.48 (t, 2H), 2.96 (s, 3H), 2.37 (t, 2H), 2.17 (s, 6H).

5-[(2-Dimethylamino-ethyl)-methyl-amino]-2'-methyl-biphenyl-3-carbaldehyde

- 15 General Procedure G gave the title compound as yellow oil in 62% yield.

¹H NMR (DMSO-d₆): δ 9.96 (s, 1H), 7.31-7.22 (m, 4H), 7.15 (dd, 1H), 7.07 (t, 1H), 6.90 (dd, 1H), 3.50 (t, 2H), 2.99 (s, 3H), 2.40 (t, 2H), 2.25 (s, 3H), 2.17 (s, 6H).

3-Bromo-5-(3-dimethylamino-propylamino)-benzaldehyde

- 20 General procedure A gave the title compound as yellow oil in 60% yield.

¹H NMR (DMSO-d₆): δ 9.82 (s, 1H), 7.14 (t, 1H), 7.02-7.00 (m, 1H), 6.37 (t, 1H), 3.07 (q, 2H), 2.28 (t, 2H), 2.13 (s, 6H), 1.66 (p, 2H).

5-(3-Dimethylamino-propylamino)-2'-methyl-biphenyl-3-carbaldehyde

- 25 General Procedure G gave the title compound as brown oil in 100% yield.

¹H NMR (DMSO-d₆): δ 9.91 (s, 1H), 7.31-7.19 (m, 4H), 7.01 (d, 2H), 6.81 (t, 1H), 6.13 (t, 1H), 3.11 (q, 2H), 2.32 (t, 2H), 2.24 (s, 3H), 2.14 (s, 6H), 1.69 (p, 2H).

3-Bromo-5-(4-methyl-[1,4]diazepan-1-yl)-benzaldehyde

- 30 General procedure A gave the title compound as brown oil in 69% yield.

¹H NMR (DMSO-d₆): δ 9.87 (s, 1H), 7.20-7.18 (m, 2H), 7.11 (t, 1H), 3.56 (t, 2H), 3.47 (t, 2H), 2.60 (t, 2H), 2.44 (t, 2H), 2.25 (s, 3H), 1.88 (p, 2H).

2'-Methyl-5-(4-methyl-[1,4]diazepan-1-yl)-biphenyl-3-carbaldehyde

- 35 General Procedure G gave the title compound as yellow oil in 52% yield.

¹H NMR (DMSO-d₆): δ 9.96 (s, 1H), 7.31-7.22 (m, 4H), 7.17 (dd, 1H), 7.04 (t, 1H), 6.90 (dd, 1H), 3.59 (t, 2H), 3.51 (t, 2H), 2.63 (t, 2H), 2.47 (t, 2H), 2.26 (s, 3H), 2.25 (s, 3H), 1.91 (p, 2H).

- 40 **2-(4-Methyl-piperazin-1-ylmethyl)-benzaldehyde**

General procedure F gave the title compound as brown oil in 80 % yield.

¹H-NMR (CDCl₃): δ 10.41 (s, 1H), 7.87 (d, 1H), 7.51 (dt, 1H), 7.41 (t, 1H), 7.38 (d, 1H), 3.81 (s, 2H), 2.6-2.3 (m, 8H), 2.27 (s, 3H).

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- 45 **4-Diethylaminomethyl-benzaldehyde**

General procedure F gave the title compound as brown oil in 74% yield.

¹H-NMR (CDCl₃): δ 10.02 (s, 1H), 7.85 (d, 2H), 7.55 (d, 2H), 3.66 (s, 2H), 2.56 (q, 4H), 1.07 (t, 6H).

5 **2-(3-Bromo-4-methoxy-phenyl)-2-methyl-propionitrile**

A solution of 2-(4-methoxy-phenyl)-2-methyl-propionitrile (17.5 g, 0.10 mol) in TFA (80 mL) was cooled to 0°C. N-bromosuccinimide (17.8 g, 0.10 mol) was added in small portions keeping the temperature below 5°C. The orange solution was stirred for 2h/25°C and evaporated to dryness. Water (200 mL) was added and the mixture was stirred vigorously for 1 h. The crude product was filtered off and recrystallized from boiling MeOH. The pure product was isolated as white needles. Yield: 19.3 g (76%). GCMS: > 99%
10 ¹H-NMR (DMSO-d₆): δ 7.68 (d, 1H), 7.50 (dd, 1H), 7.16 (d, 1H), 3.86 (s, 3H), 1.70 (s, 6H).

15 **2-(3-Bromo-4-methoxy-phenyl)-2-methyl-propionaldehyde**

A solution of 2-(3-bromo-4-methoxy-phenyl)-2-methyl-propionitrile (12.71 g, 0.050 mol) in dry THF (100 mL) was cooled to -10°C under argon. DIBALH (1M in THF, 100 mL, 0.10 mol) was added keeping the temperature below 0°C. The mixture was stirred for 30 min/0°C and then 2 h/25°C. The clear solution was carefully poured into Icecold
20 hydrochloric acid (2M, 100 mL). The THF was removed under reduced pressure to give clear oil. The oil was distilled (b.p. 114-130 °C/ 4.3 x 10⁻³ mbar) Yield: 7.40 g (58%). GCMS: > 99%
¹H-NMR (CDCl₃): δ 9.44 (s, 1H), 7.45 (d, 1H), 7.15 (dd, 1H), 6.90 (d, 1H), 3.89 (s, 3H), 1.43 (s, 6H).

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2-Bromo-4-(1,1-dimethyl-allyl)-1-methoxy-benzene

A suspension of methyltriphenylphosphonium bromide (7.71 g, 0.0215 mol) in dry THF (100 mL) was cooled to 0°C under argon. *n*-BuLi (2.5M, 8 mL, 0.020 mol) was added slowly. The resulting clear orange solution of the ylide was stirred for another 15 min at
30 0°C. 2-(3-Bromo-4-methoxy-phenyl)-2-methyl-propionaldehyde (3.7 g, 0.014 mol) was dissolved in dry THF (50 mL) and added to ylide-solution. The mixture was stirred for 3h/25°C and the resulting suspension was quenched with MeOH (10 mL). The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using *n*-heptane as eluent. Yield: 3.1 g (84%). GCMS: > 99%
35 ¹H-NMR (CDCl₃): δ 7.50 (d, 1H), 7.23 (dd, 1H), 6.83 (d, 1H), 5.97 (dd, 1H), 5.06 (dd, 1H), 5.02 (dd, 1H), 3.87 (s, 3H), 1.44 (s, 6H).

5-(1,1-Dimethyl-allyl)-2-methoxy-benzaldehyde

To a solution of 2-Bromo-4-(1,1-dimethyl-allyl)-1-methoxy-benzene (3.1 g, 0.012 mol) in
40 dry THF (50 mL) was cooled to -78°C under argon. *n*-BuLi (2.5M, 5.1 mL, 0.0128 mol) was added keeping the temperature below -70°C. The yellow mixture was stirred for another 15 min and quenched with dry DMF (1.4 mL, 0.018 mol). The cooling bath was removed and the mixture was allowed to warm to 25°C. A saturated solution of NaHCO₃ (30 mL)

was added and then extracted with EtOAc (3 x 50 mL). The organic phase was dried (Na₂SO₄) and evaporated to yellow oil. Yield: 2.31 g (94%).

¹H-NMR (CDCl₃): δ 10.48 (s, 1H), 7.84 (d, 1H), 7.55 (dd, 1H), 6.94 (d, 1H), 6.00 (dd, 1H), 5.05 (dd, 1H), 5.01 (dd, 1H), 3.93 (s, 3H), 1.41 (s, 6H).

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1-(3-Diethoxymethyl-phenyl)-piperazine

Prepared by general procedure A gave the title compound as brown oil in 69% yield.

¹H-NMR (CDCl₃): δ 7.26 (t, 1H), 7.08 (t, 1H), 6.96 (bd, 1H), 6.89 (dd, 1H), 3.70-3.40 (m, 4H), 3.18 (t, 4H), 3.06 (t, 4H), 1.22 (t, 6H).

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3-[4-(2-Methoxy-acetyl)-piperazin-1-yl]-benzaldehyde

Prepared by general procedure M using 1-(3-diethoxymethyl-phenyl)-piperazine. Acidic work-up gave the free benzaldehyde in 86% yield as yellow oil.

¹H-NMR (CDCl₃): δ 9.97 (s, 1H), 7.48 (t, 1H), 7.43-7.37 (m, 2H), 7.20 (dq, 1H), 4.16 (s, 2H), 3.81 (t, 2H), 3.70 (t, 2H), 3.43 (s, 3H), 3.26 (t, 4H).

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3-[4-(2-Dimethylamino-acetyl)-piperazin-1-yl]-benzaldehyde

Prepared by general Procedure H gave the title compound as brown oil in 53% yield.

¹H-NMR (CDCl₃): δ 9.96 (s, 1H), 7.46-7.34 (m, 3H), 7.19 (dd, 1H), 3.79 (q, 4H), 3.24 (q, 4H), 3.16 (s, 2H), 2.29 (s, 6H).

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3-Fluoro-2'-methoxy-biphenyl-4-carbaldehyde

Prepared by general Procedure G gave the title compound as brown oil in 96% yield.

¹H-NMR (CDCl₃): δ 10.40 (s, 1H), 7.92 (t, 1H), 7.50-7.34 (m, 4H), 7.07 (td, 1H), 7.03 (bd, 1H), 3.85 (s, 3H).

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2'-Methoxy-3-(4-methyl-piperazin-1-yl)-biphenyl-4-carbaldehyde

Prepared by general procedure B gave the title compound as yellow oil in 47% yield.

¹H-NMR (DMSO-d₆): δ 10.20 (s, 1H), 7.72 (d, 1H), 7.43-7.36 (m, 2H), 7.37-7.23 (m, 2H), 7.15 (bd, 1H), 7.06 (bt, 1H), 3.79 (s, 3H), 3.09 (t, 4H), 2.52 (t, 4H), 2.25 (s, 3H).

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3-Bromo-4-(4-methyl-piperazin-1-yl)-benzaldehyde

Prepared by general procedure B gave the title compound as yellow oil in 42% yield.

¹H-NMR (CDCl₃): δ 9.87 (s, 1H), 8.06 (d, 1H), 7.78 (dd, 1H), 7.12 (d, 1H), 3.22 (t, 4H), 2.65 (t, 4H), 2.38 (s, 3H).

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6-(4-Methyl-piperazin-1-yl)-biphenyl-3-carbaldehyde

Prepared by general Procedure G gave the title compound as yellow oil in 99% yield.

¹H-NMR (CDCl₃): δ 9.91 (s, 1H), 7.79 (dd, 1H), 7.73 (d, 1H), 7.65-7.55 (m, 2H), 7.48-7.41 (m, 2H), 7.35 (td, 1H), 7.12 (d, 1H), 3.02 (t, 4H), 2.36 (t, 4H), 2.28 (s, 3H).

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2-(2-Chloro-4-methoxy-phenyl)propionitrile

A solution of 2'-chloro-4'-methoxyacetophenone (18.5 g, 0.10 mol) and tosylmethylisocyanide (TOSMIC, 21.5 g, 0.11 mol) in dry 1,2-dimethoxyethane (100 mL) was cooled to -10°C. A solution of *t*-BuOK (22.4 g, 0.20 mol) in dry *t*-BuOH (250 mL) was

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added slowly keeping the temperature below 5°C. The homogeneous orange solution was stirred for 2h/0°C and 1h/25°C. The resulting suspension was evaporated to a slurry. Water (200 mL) was added and extracted with Et₂O (3 x 150 mL). The organic phase was dried (Na₂SO₄) and the solvent was removed under reduced pressure leaving an orange

5 oil. Yield: 19 g (97%). GCMS: > 98 %

¹H-NMR (DMSO-d₆): δ 7.49 (d, 1H), 7.12 (d, 1H), 7.02 (dd, 1H), 4.42 (q, 1H), 3.80 (s, 3H), 1.55 (d, 3H).

2-(2-Chloro-4-methoxy-phenyl)-2-methyl-propionitrile

10 A solution of 2-(2-chloro-4-methoxy-phenyl)propionitrile (19 g, 0.097 mol) and methyl iodide (7 mL, 0.11 mol) in dry DMF (100 mL) was flushed with argon for 2 min and cooled to 0°C. Sodium hydride (60% oil susp., 4.4 g, 0.11 mol) was added in small portions. The thick suspension was stirred for another 18h at 25°C and then poured into

15 (Na₂SO₄) and the solvent was removed under reduced pressure leaving a yellow oil which was distilled. Bp: 103-106°C/0.06 mbar, clear oil that solidifies on standing. Yield: 17.5 g (83%). GCMS: > 99%

¹H-NMR (DMSO-d₆): δ 7.43 (d, 1H), 7.13 (d, 1H), 6.98 (dd, 1H), 3.80 (s, 3H), 1.77 (s, 6H).

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2-(5-Bromo-2-chloro-4-methoxy-phenyl)-2-methyl-propionitrile

A solution of 2-(2-chloro-4-methoxy-phenyl)-2-methyl-propionitrile (17.5 g, 0.0835 mol) in TFA (100 mL) was cooled to 0°C. N-bromosuccinimide (14.9 g, 0.0835 mol) was added in small portions keeping the temperature below 5°C. The orange solution was stirred for

25 2h/25°C and evaporated to dryness. Water (200 mL) was added and the mixture was stirred vigorously for 1 h. The crude product was filtered off and recrystallized from boiling MeOH. The pure product was isolated as white needles. Yield: 13 g (54%). GCMS: > 99%

¹H-NMR (DMSO-d₆): δ 7.56 (s, 1H), 7.23 (s, 1H), 3.84 (s, 3H), 1.70 (s, 6H).

30 2-(5-Bromo-2-chloro-4-methoxy-phenyl)-2-methyl-propionaldehyde

A solution of 2-(5-bromo-2-chloro-4-methoxy-phenyl)-2-methyl-propionitrile (13 g, 0.045 mol) in dry THF (80 mL) was cooled to -10°C under argon. DIBALH (1M in THF, 100 mL, 0.10 mol) was added keeping the temperature below 0°C. The mixture was stirred for 30 min/0°C and then 2 h/25°C. The clear solution was carefully poured into icecold

35 hydrochloric acid (2M, 100 mL). The THF was removed under reduced pressure. The aqueous phase was cooled and the crude product was filtered off and recrystallized from boiling MeOH. Yield: 7.8 g (59%). GCMS: > 99%

¹H-NMR (DMSO-d₆): δ 9.61 (s, 1H), 7.68 (s, 1H), 7.27 (s, 1H), 3.89 (s, 3H), 1.40 (s, 6H).

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1-Bromo-4-chloro-5-(1,1-dimethyl-allyl)-2-methoxy-benzene

A suspension of methyltriphenylphosphonium bromide (11.4 g, 0.032 mol) in dry THF (100 mL) was cooled to 0°C under argon. *n*-BuLi (2.5M, 12 mL, 0.030 mol) was added slowly. The suspension became more homogenous. The resulting clear orange solution of the ylide

was stirred for another 15 min at 0°C. 2-(5-Bromo-2-chloro-4-methoxy-phenyl)-2-methyl-propionaldehyde (7.8 g, 0.027 mol) was dissolved in dry THF (50 mL) and added to ylide-solution. The mixture was stirred for 3h/25°C and the resulting suspension was quenched with MeOH (10 mL). The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using *n*-heptane as eluent. Yield: 3.92 g (50%). GCMS: > 99%

¹H-NMR (DMSO-d₆): δ 7.55 (s, 1H), 7.14 (s, 1H), 6.05 (dd, 1H), 5.04 (dd, 1H), 4.92 (dd, 1H), 3.87 (s, 3H), 1.45 (s, 6H).

10 4-Chloro-5-(1,1-dimethyl-allyl)-2-methoxy-benzaldehyde

To a solution of 1-bromo-4-chloro-5-(1,1-dimethyl-allyl)-2-methoxy-benzene (3.92 g, 0.0135 mol) in dry THF (30 mL) was cooled to -78°C under argon. *n*-BuLi (2.5M, 6 mL, 0.0145 mol) was added keeping the temperature below -70°C. The yellow mixture was stirred for another 15 min and quenched with dry DMF (1.2 mL, 0.015 mol). The cooling bath was removed and the mixture was allowed to warm to 25°C. A saturated solution of NaHCO₃ (30 mL) was added and then extracted with EtOAc (3 x 50 mL). The organic phase was dried (Na₂SO₄) and evaporated to dryness. The crude product was recrystallized from MeOH. Yield: 3.00 g (93%). GCMS: > 99%

¹H-NMR (DMSO-d₆): δ 10.30 (s, 1H), 7.80 (s, 1H), 7.30 (s, 1H), 6.08 (dd, 1H), 5.06 (dd, 1H), 4.91 (dd, 1H), 3.93 (s, 3H), 1.49 (s, 6H).

1-Biphenyl-4-ylmethyl-4-methyl-piperazine

General Procedure G gave the title compound as yellow oil in 77% yield.

¹H-NMR (CDCl₃): δ 7.63-7.55 (m, 5H), 7.48-7.38 (m, 4H), 3.58 (s, 2H), 2.55 (bs, 8H), 2.35 (s, 3H).

4-(4-Methyl-piperazin-1-ylmethyl)-biphenyl-3-carbaldehyde

A solution of 1-biphenyl-4-ylmethyl-4-methyl-piperazine (26 mmol) in diethyl ether (50 mL) was added *n*-BuLi (38 mmol) and DMF (15 mL) and was refluxed for 6h. The reaction was cooled and added 2 N NaOH (50 mL) and extracted with diethyl ether. Evaporation *in vacuo* gave a black oil that was purified by flash chromatography. Yield: 28% as black oil.

¹H-NMR (CDCl₃): δ 10.49 (s, 1H), 8.14 (d, 1H), 7.76 (dd, 1H), 7.66-7.63 (m, 2H), 7.51-7.40 (m, 4H), 3.90 (bs, 2H), 2.64 (bs, 8H), 2.38 (bs, 3H).

35 2'-Methyl-4-(4-pyrrolidin-1-yl-piperidin-1-yl)-biphenyl-3-carbaldehyde

General procedure B gave the title compound as yellow oil in 37% yield.

¹H-NMR (CDCl₃): δ 10.47 (s, 1H), 7.91 (d, 1H), 7.62 (dd, 1H), 7.41-7.33 (m, 4H), 7.29 (d, 1H), 3.54 (d, 2H), 3.16-3.07 (m, 2H), 2.90 (bs, 4H), 2.41 (s, 3H), 2.23 (bs, 2H), 2.03 (bs, 7H).

2'-Methyl-4-[methyl-(1-methyl-piperidin-4-yl)-amino]-biphenyl-3-carbaldehyde

General procedure B gave the title compound as an yellow oil in 19% yield.

¹H-NMR (CDCl₃): δ 10.10 (s, 1H), 7.61 (d, 1H), 7.30 (dd, 1H), 7.11-7.01 (m, 5H), 2.94-2.80 (m, 3H), 2.69 (s, 3H), 2.12 (s, 3H), 1.88 (s, 3H), 1.87-1.68 (m, 6H).

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4-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-2'-methyl-biphenyl-3-carbaldehyde

General procedure B gave the title compound as yellow oil in 31% yield.

¹H-NMR (CDCl₃): δ 10.35 (s, 1H), 7.80 (d, 1H), 7.53 (dd, 1H), 7.30-7.17 (m, 5H), 3.77 (t, 2H), 3.28 (t, 4H), 2.91 (bs, 4H), 2.79 (t, 2H), 2.30 (s, 3H).

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4-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-2'-methoxy-biphenyl-3-carbaldehyde

General procedure B gave the title compound as yellow oil in 31% yield.

¹H-NMR (CDCl₃): δ 10.36 (s, 1H), 8.00 (d, 1H), 7.76 (dd, 1H), 7.33 (d, 2H), 7.17 (d, 1H), 7.07-6.99 (m, 2H), 3.84 (s, 3H), 3.72 (t, 2H), 3.22 (t, 4H), 2.80 (t, 4H), 2.70 (t, 2H).

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2-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-benzaldehyde

General procedure B gave the title compound as yellow oil in 7% yield.

¹H-NMR (CDCl₃): δ 10.34 (s, 1H), 7.83 (dd, 1H), 7.58-7.52 (m, 1H), 7.28-7.12 (m, 2H), 3.70 (t, 2H), 3.16 (t, 4H), 2.77 (t, 4H), 2.68 (t, 2H).

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2-Fluoro-5-pyridin-2-yl-benzaldehyde

General Procedure G using 2-bromopyridin and 4-fluoro-3-formylbenzeneboronic acid gave the title compound as colourless crystals in 64% yield.

¹H-NMR (CDCl₃): δ 10.44 (s, 1H), 8.71 (dd, 1H), 8.47 (dd, 1H), 8.41-8.35 (m, 1H), 7.84-7.76 (m, 2H), 7.31-7.27 (m, 2H).

25

2-(4-Methyl-piperazin-1-yl)-5-pyridin-2-yl-benzaldehyde

General procedure B gave the title compound as an yellow oil in 27% yield.

¹H-NMR (CDCl₃): δ 10.34 (s, 1H), 8.67 (dt, 1H), 8.39 (d, 1H), 8.26 (dd, 1H), 7.76-7.74 (m, 2H), 7.24-7.20 (m, 2H), 3.21 (t, 4H), 2.67 (t, 4H), 2.40 (s, 3H).

30

2'-Methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-carbaldehyde

General Procedure G gave the title compound as an yellow oil in 84% yield.

¹H-NMR (CDCl₃): δ 10.36 (s, 1H), 7.99 (d, 1H), 7.75 (dd, 1H), 7.33 (d, 2H), 7.18 (d, 1H), 7.07-6.99 (m, 2H), 3.84 (s, 3H), 3.22 (t, 4H), 2.70 (t, 4H), 2.43 (s, 3H).

35

2-(4-Acetyl-piperazin-1-yl)-5-bromo-benzaldehyde

General procedure B gave the title compound as yellow crystals in 35% yield.

¹H-NMR (CDCl₃): δ 10.11 (s, 1H), 7.77 (d, 1H), 7.48 (dd, 1H), 6.83 (d, 1H), 3.66 (t, 2H), 3.51 (t, 2H), 2.89 (q, 4H), 1.99 (s, 3H).

40

4-(4-Acetyl-piperazin-1-yl)-2'-methoxy-biphenyl-3-carbaldehyde

General Procedure G gave the title compound as yellow crystals in 57% yield.

¹H-NMR (CDCl₃): δ 10.38 (s, 1H), 8.01 (d, 1H), 7.77 (dd, 1H), 7.38-7.31 (m, 2H), 7.15 (d, 1H), 7.08-7.00 (m, 2H), 3.86 (t, 2H), 3.84 (s, 3H), 3.71 (t, 2H), 3.16-3.11 (m, 4H), 2.18 (s, 3H).

5 **4-(4-Bromo-2-formyl-phenyl)-piperazine-1-carboxylic acid tert-butyl ester**

General procedure B gave the title compound as an yellow oil in 39% yield.

¹H-NMR (CDCl₃): δ 10.30 (s, 1H), 7.96 (d, 1H), 7.66 (d, 1H), 7.03 (d, 1H), 3.66 (t, 4H), 3.05 (t, 4H), 1.52 (s, 9H).

10 **5-Bromo-2-(4-methyl-[1,4]diazepan-1-yl)-benzaldehyde**

General procedure B gave the title compound as an yellow oil in 89% yield.

¹H-NMR (CDCl₃): δ 10.10 (s, 1H), 7.83 (d, 1H), 7.48 (dd, 1H), 6.95 (d, 1H), 3.55-3.46 (m, 5H), 2.76-2.67 (m, 5H), 2.41 (s, 3H).

15 **4-[(3-Dimethylamino-propyl)-methyl-amino]-2'-methyl-biphenyl-3-carbaldehyde**

General procedure B gave the title compound as an yellow oil in 85% yield.

¹H-NMR (CDCl₃): δ 10.17 (s, 1H), 7.59 (d, 1H), 7.53 (dd, 1H), 7.30-7.20 (m, 5H), 3.21 (t, 2H), 2.90 (s, 3H), 2.24 (s, 3H), 2.19 (t, 2H), 2.07 (s, 6H).

20 **4-[(2-Dimethylamino-ethyl)-methyl-amino]-2'-methyl-biphenyl-3-carbaldehyde**

General procedure B gave the title compound as yellow oil in 43% yield.

¹H-NMR (CDCl₃): δ 10.32 (s, 1H), 7.77 (d, 1H), 7.48 (dd, 1H), 7.28-7.22 (m, 4H), 7.20 (d, 1H), 3.34 (t, 2H), 2.99 (s, 3H), 2.64 (t, 2H), 2.31 (s, 3H), 2.30 (s, 3H).

25 **3',5'-Dimethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-carbaldehyde**

General Procedure G gave the title compound as yellow crystals in 74% yield.

¹H-NMR (DMSO-d₆): δ 10.22 (s, 1H), 7.91 (d, 1H), 7.87 (dd, 1H), 7.28-7.24 (m, 3H), 6.98 (bs, 1H), 3.12 (t, 4H), 2.56 (t, 4H), 2.33 (s, 6H), 2.25 (s, 3H).

30 **2'-Methyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-carbaldehyde**

General Procedure G gave the title product as brown oil in 80% yield.

¹H-NMR (CDCl₃) δ 10.36 (s, 1H), 7.78 (d, 1H), 7.50 (dd, 1H), 7.27-7.19 (m, 4H), 7.16 (d, 1H), 3.19 (t, 4H), 2.67 (t, 4H), 2.41 (s, 3H), 2.27 (s, 3H).

35 **2'-Methoxy-3-(4-methyl-[1,4]diazepan-1-yl)-biphenyl-4-carbaldehyde**

General procedure B gave the title product as yellow oil in 47% yield.

¹H-NMR (DMSO-d₆) δ 10.07 (s, 1H), 7.66 (d, 1H), 7.41-7.33 (m, 2H), 7.18 (d, 1H), 7.13 (d, 1H), 7.07-7.01 (m, 2H), 3.78 (s, 3H), 3.44-3.53 (m, 4H), 2.66 (t, 2H), 2.57 (t, 2H), 2.27 (s, 3H), 1.88 (p, 2H).

40

4-Bromo-2-(4-methyl-piperazin-1-yl)-benzaldehyde

General procedure B gave the title product as brown oil in quantitative yield.

¹H-NMR (CDCl₃) δ 10.21 (s, 1H), 7.64 (d, 1H), 7.25-7.21 (m, 2H), 3.14-3.09 (m, 4H), 2.63-2.58 (m, 4H), 2.36 (s, 3H).

45

N-(3-Acetyl-phenyl)-2-(4-methyl-piperazin-1-yl)-acetamide

General Procedure H gave the title compound as brown oil in 73% yield.

¹H-NMR (CDCl₃): δ 9.25 (s, 1H), 8.05-7.98 (m, 1H), 7.71 (dt, 1H), 7.46 (t, 1H), 3.19 (s, 2H), 2.68 (t, 4H), 2.63 (s, 3H), 2.56 (b, 4H), 2.38 (s, 3H).

5

1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}ethanone

General procedure C gave the title compound as yellow oil in 62% yield ref. 3.

¹H-NMR (CDCl₃): δ 7.72 (d, 2H), 6.73 (d, 2H), 3.53 (t, 2H), 3.08 (s, 3H), 2.50 (t, 2H), 2.48 (s, 3H), 2.30 (s, 6H).

10

1-[4-(2-Dimethylamino-ethylamino)-phenyl]ethanone

General procedure C gave the title compound as yellow oil in 92% yield ref. 3

¹H-NMR (CDCl₃): δ 7.80 (d, 2H), 6.54 (d, 2H), 5.29 (s, br, 1H), 3.33-3.24 (m, 2H), 2.57 (t, 2H), 2.56 (s, 3H), 2.31 (s, 6H).

15

1-[4-(3-Dimethylamino-propylamino)-phenyl]ethanone

General procedure C gave the title compound as yellow oil in 56% yield

¹H-NMR (CDCl₃): δ 7.81 (d, 2H), 6.54 (d, 2H), 5.31 (s, br, 1H), 3.25 (t, 2H), 2.48 (s, 3H), 2.41 (t, 2H), 2.25 (s, 6H), 1.79 (m, 2H).

20

1-[3-(2-Dimethylamino-ethylamino)-phenyl]ethanone

General procedure C gave the title compound as yellow oil in 73% yield

¹H-NMR (CDCl₃): δ 7.28-7.18 (m, 3H), 6.85-6.78 (m, 1H), 4.45 (s, br, 1H), 4.10-3.23 (m, 2H), 2.59-2.52 (m, 5H), 2.25 (s, 6H).

25

1-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}ethanone

General procedure C gave the title compound as yellow oil in 62% yield

¹H-NMR (CDCl₃): δ 7.30-7.18 (m, 3H), 6.82-6.78 (m, 1H), 3.56 (t, 2H), 3.05 (s, 3H), 2.55 (t, 2H), 2.48 (s, 3H), 2.38 (s, 6H).

30

1-[2-(2-Dimethylamino-ethylamino)-phenyl]ethanone

General procedure D gave the title compound as yellow oil in 58% yield

¹H-NMR (CDCl₃): δ 8.95 (s, br, 1H), 7.76-7.71 (dd, 1H), 7.38-7.31 (d, 1H), 6.73-6.66 (d, 1H), 6.61-6.55 (td, 1H), 3.33-3.24 (m, 2H), 2.58 (t, 2H), 2.56 (s, 3H), 2.30 (s, 6H).

35

1-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}ethanone

General procedure D gave the title compound as yellow oil in 93 % yield

¹H-NMR (CDCl₃): δ 7.42-7.32 (m, 2H), 7.07 (d, 1H), 7.70-6.93 (td, 1H), 3.17 (t, 2H), 2.80 (s, 3H), 2.61 (s, 3H), 2.49-2.42 (m, 2H), 2.20 (s, 6H).

40

1-[2-(3-Dimethylamino-propylamino)-phenyl]ethanone

General procedure D gave the title compound as yellow oil in 45% yield

¹H-NMR (CDCl₃): δ 8.91 (s, br, 1H), 7.74-7.70 (dd, 1H), 7.38-7.31 (d, 1H), 6.73-6.65 (d, 1H), 6.61-6.55 (td, 1H), 3.25 (t, 2H), 2.48 (s, 3H), 2.41 (t, 2H), 2.25 (s, 6H), 1.79 (m, 2H).

5 **1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-ethanone**

General procedure E gave the title compound as brown oil in 78% yield.

¹H-NMR (CDCl₃): δ 7.42-7.29 (m, 4H), 3.65 (s, 2H), 2.54 (s, 3H), 2.43 (b, 8H), 2.27 (s, 3H).

10 **N-(3-Acetyl-phenyl)-2-dimethylamino-acetamide**

General Procedure H gave the title compound as brown oil in 85% yield

¹H-NMR (CDCl₃): δ 9.31 (s, 1H), 8.05 (m, 2H), 7.72 (dt, 1H), 7.46 (t, 1H), 3.11 (s, 2H), 2.62 (s, 3H), 2.41 (s, 6H).

15 **N-(4-Acetyl-phenyl)-N-(2-dimethylamino-ethyl)-acetamide**

Prepared by general procedure M gave the title compound as brown oil in 75% yield.

¹H-NMR (CDCl₃): δ 8.02 (d, 2H), 7.35 (d, 2H), 3.86 (t, 2H), 2.64 (s, 3H), 2.43 (t, 2H), 2.25 (s, 6H), 1.88 (s, 3H).

1-[4-Methoxy-2-(4-methyl-piperazin-1-yl)-phenyl]-ethanone

20 General procedure D gave the title compound as yellow oil in 49% yield.

¹H-NMR (CDCl₃): δ 7.53 (d, 1H), 6.59-6.56 (m, 2H), 3.85 (s, 3H), 3.05 (t, 4H), 2.65-2.61 (m, 7H), 2.38 (s, 3H).

Propane-1-sulfonic acid (2-acetyl-phenyl)-amide

25 A solution of the aniline (111 mmol) and TEA (222 mmol) in dry CH₂Cl₂ (200 mL) was cooled on ice and slowly added propane-1-sulfonyl chloride (133 mmol) in dry CH₂Cl₂ (50 mL). The reaction was heated to room temperature and left over night. The organic phase was washed with water and a solution of 2 N HCl and evaporated in vacuo.

Recrystallization (EtOAc/heptane) gave the desired product. Yield: 64% as yellow crystals.

30 ¹H-NMR (CDCl₃): δ 11.31 (bs, 1H), 7.94 (dd, 1H), 7.80 (dd, 1H), 7.57 (dt, 1H), 7.15 (dt, 1H), 3.17-3.12 (m, 2H), 2.69 (s, 3H), 1.89-1.81 (m, 2H), 1.02 (t, 3H).

1-[2-Fluoro-6-(4-methyl-piperazin-1-yl)-phenyl]-ethanone

General procedure D gave the title compound as orange oil in 38% yield.

35 ¹H-NMR (CDCl₃): δ 7.35-7.28 (m, 1H), 6.90 (d, 1H), 6.84 (dt, 1H), 3.07 (t, 4H), 2.59 (bs, 7H), 2.39 (s, 3H).

1-[2,6-Bis-(4-methyl-piperazin-1-yl)-phenyl]-ethanone

General procedure D starting from 2,6-difluoroacetophenone and using DMSO as the

40 solvent gave the title compound as orange crystals in 61% yield.

¹H-NMR (DMSO-d₆): δ 7.28 (t, 1H), 6.90 (d, 2H), 2.85 (t, 8H), 2.34 (bs, 8H), 2.32 (s, 3H), 2.18 (s, 6H).

1-[2,4-Bis-(4-methyl-piperazin-1-yl)-phenyl]-ethanone

General procedure D starting from 2,6-difluoroacetophenone using DMSO as the solvent gave the title compound as orange crystals in 93% yield.

¹H-NMR (CDCl₃): δ 7.36 (d, 1H), 6.56 (dd, 1H), 6.47 (d, 1H), 3.25 (t, 4H), 2.92 (t, 4H),
5 2.51 (s, 3H), 2.47 (t, 4H), 2.41 (t, 4H), 2.22 (s, 3H), 2.21 (s, 3H).

1-[2-(4-Methyl-piperazin-1-yl)-phenyl]-ethanone

General procedure D gave the title compound as yellow oil in 65% yield.

¹H-NMR (CDCl₃): δ 7.41 (m, 2H), 7.07-7.01 (m, 2H), 3.03 (t, 4H), 2.63 (s, 3H), 2.58 (t,
10 4H), 2.35 (s, 3H).

1-[2-Fluoro-4-(tetrahydro-pyran-2-yloxy)-phenyl]-ethanone

A solution of 1-(2-fluoro-4-hydroxy-phenyl)-ethanone (130 mmol), 3,4-dihydro-2H-pyran (260 mmol) and a catalytic amount of pyridinium p-toluenesulfonate in CH₂Cl₂ (200 mL)
15 was left overnight at room temperature. The organic phase was washed with 1 N NaOH (aq) (1 x 50 mL) and dried (K₂CO₃). Evaporation *in vacuo* gave a brown oil, that was purified by vacuum distillation. The desired product was isolated as clear oil in 74% yield: bp: 130-140°C/0.05 mbar.

¹H-NMR (CDCl₃): δ 7.86 (t, 1H), 6.87 (dd, 1H), 6.82 (dd, 1H), 5.49 (t, 1H), 3.86-3.78 (m,
20 1H), 3.67-3.61 (m, 1H), 2.59 (d, 3H), 1.97-1.60 (m, 6H).

1-[2-(4-Methyl-piperazin-1-yl)-4-(tetrahydro-pyran-2-yloxy)-phenyl]-ethanone

General procedure D gave the title compound as yellow oil in 66% yield.

¹H-NMR (CDCl₃): δ 7.36 (d, 1H), 6.72-6.67 (m, 2H), 5.55 (t, 1H), 3.75-3.71 (m, 1H),
25 3.59-3.55 (m, 1H), 2.91 (t, 4H), 2.54 (s, 3H), 2.53-2.45 (m, 4H), 2.23 (s, 3H), 1.85-1.53 (m, 6H).

1-(3-Dimethylaminomethyl-4-methoxy-phenyl)-ethanone

(5-Bromo-2-methoxy-benzyl)-dimethyl-amine (29 mmol), Butoxy-ethene (100 mmol),
30 Palladium acetate (0.9 mmol), 1,3-Bis(diphenylphosphino) propane (1.8 mmol), and potassium carbonate were suspended in DMF (50 ml) and H₂O under argon. Heated at 80 °C overnight. Poured into hydrochloric acid (2 M) and stirred for 1 hour. The mixture was adjusted to basic pH and extracted with CH₂Cl₂. The organic phase was evaporated on celite and the residue was purified by flash chromatography to give the title product as
35 orange oil in 42% yield.

¹H-NMR (CDCl₃) δ 7.90 (s, 1H), 7.88 (dd, 1H), 6.89 (d, 1H), 3.88 (s, 3H), 3.44 (s, 2H), 2.55 (s, 3H), 2.25 (s, 6H).

1-(3-Dimethylaminomethyl-phenyl)-ethanone

40 General procedure E gave the title product as yellow oil in 89% yield.

¹H-NMR (CDCl₃) δ 7.89 (s, 1H), 7.85 (d, 1H), 7.52 (d, 1H), 7.42 (t, 1H), 3.47 (s, 2H), 2.61 (s, 3H), 2.25 (s, 6H).

1-(2-[(2-Dimethylamino-ethyl)-methyl-amino]-methyl)-phenyl)-ethanone

General procedure E gave the title product as brown oil in 88% yield.

¹H-NMR (DMSO-d₆) δ 7.51 (d, 1H), 7.40-7.30 (m, 3H), 3.57 (s, 2H), 2.56 (s, 3H), 2.39-2.32 (m, 2H), 2.29-2.23 (m, 2H), 2.07 (s, 6H), 2.03 (s, 3H).

5 **1-{2-[(tert-Butyl-methyl-amino)-methyl]-phenyl}-ethanone**

General procedure E gave the title product as brown oil in 44% yield.

¹H-NMR (DMSO-d₆) δ 7.52 (dd, 1H), 7.51 (dd, 1H), 7.40 (td, 1H), 7.30 (td, 1H), 3.63 (s, 2H), 2.48 (s, 3H), 1.91 (s, 3H), 1.03 (s, 9H).

10 **3-(2,4-Dichlorophenyl)-1-(4-fluorophenyl)propan-1-one:**

General Procedure K gave the title compound as colourless crystals in 53 % yield.

¹H-NMR (DMSO-d₆): δ 8.12-8.04 (m, 2H), 7.58 (d, 1H), 7.46 (d, 1H), 7.40-7.30 (m, 3H), 3.37 (t, 2H), 3.02 (t, 2H).

15 **(E)-4-{4-Bromo-2-[3-(2-fluoro-4-methoxy-phenyl)-3-oxo-propenyl]-phenyl}-piperazine-1-carboxylic acid tert-butyl ester**

General Procedure I gave the title compound as yellow oil in 53% yield.

¹H NMR (CDCl₃) δ 7.90 (t, 2H), 7.77 (d, 1H), 7.42 (dd, 1H), 6.93 (d, 1H), 6.76 (dd, 1H), 6.68 (dd, 1H), 6.63 (dd, 1H), 3.88 (s, 3H), 3.62 (t, 4H), 2.91 (bs, 4H), 1.49 (s, 9H).

20

(E)-3-[5-Bromo-2-(4-methyl-[1,4]diazepan-1-yl)-phenyl]-1-(2-fluoro-4-methoxy-phenyl)-propenone

General Procedure I gave the title compound as orange oil in 85% yield.

25 ¹H NMR (CDCl₃) δ 8.07 (dd, 1H), 7.91 (t, 1H), 7.72 (d, 1H), 7.40 (dd, 1H), 7.34 (dd, 1H), 6.98 (d, 1H), 6.82 (dd, 1H), 6.68 (dd, 1H), 3.90 (s, 3H), 3.35-2.38 (m, 4H), 2.78-2.73 (m, 4H), 2.44 (s, 3H), 1.98-1.94 (m, 2H).

B001: (E)-3-[3-(2-Dimethylamino-ethylamino)-phenyl]-1-(4-methoxy-phenyl)-propenone

- General Procedure I gave the fumaric acid salt of title compound as yellow crystals in 64 % yield. ¹H-NMR (DMSO-d₆): δ 8.14 (d, 2H), 7.81 (d, 1H), 7.59 (d, 1H), 7.16 (t, 1H), 7.12-7.00 (m, 4H), 6.73-6.68 (dd, 1H), 6.56 (s, 2H), 3.88 (s, 3H), 3.30 (t, 2H), 2.79 (t, 2H), 2.44 (s, 6H).

B002: (E)-3-(2,4-Dichloro-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

- 10 General Procedure I gave the oxalate salt of title compound as yellow crystals in 15 % yield. ¹H-NMR (DMSO-d₆): δ 8.26 (d, 1H), 8.08 (d, 2H), 8.00 (d, 1H), 7.89 (d, 1H), 7.74 (s, 1H), 7.54 (d, 1H), 6.86 (d, 2H), 3.78 (t, br, 2H), 3.12 (t, br, 2H), 3.07 (s, 3H), 2.75 (s, 6H).

B003: (E)-1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(4-fluoro-phenyl)-propenone

- General Procedure I gave the oxalate salt of title compound as yellow crystals in 12 % yield. ¹H-NMR (DMSO-d₆): δ 8.06 (d, 2H), 7.98-7.82 (m, 3H), 7.65 (d, 1H), 7.28 (t, 2H), 6.86 (d, 2H), 3.80 (t, 3H), 3.15 (t, 2H), 3.06 (s, 3H), 2.75 (s, 6H).

20

B004: (E)-3-(2,5-Difluoro-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

- General Procedure I gave the oxalate salt of title compound as yellow crystals in 12 % yield. ¹H-NMR (DMSO-d₆): δ 8.11 (m, 4H), 7.69 (d, 1H), 7.41-7.28 (m, 2H), 6.86 (d, 2H), 3.80 (t, 3H), 3.15 (t, 2H), 3.06 (s, 3H), 2.75 (s, 6H).

25

B005: (E)-3-(2-Bromo-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

- General Procedure I gave the oxalate salt of title compound as yellow crystals in 18 % yield. ¹H-NMR (DMSO-d₆): δ 8.16 (dd, 1H), 8.07 (d, 2H), 7.92 (s, 2H), 7.73 (dd, 1H), 7.48 (t, 1H), 7.40-7.36 (td, 1H), 6.86 (d, 2H), 3.79 (t, 3H), 3.11 (t, 2H), 3.04 (s, 3H), 2.74 (s, 6H).

30

B006: (E)-3-(4-Bromo-2-fluoro-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

- General Procedure I gave the oxalate salt of title compound as yellow crystals in 18 % yield. ¹H-NMR (DMSO-d₆): δ 8.12-7.96 (m, 4H), 7.72-7.64 (m, 2H), 7.56-7.50 (dd, 1H), 6.86 (d, 2H), 3.78 (t, 3H), 3.08 (t, 2H), 3.04 (s, 3H), 2.74 (s, 6H).

35

B007: (E)-3-[4-(2-Dimethylamino-ethylamino)-phenyl]-1-(4-methoxy-phenyl)-propenone

- General Procedure I gave the fumarate salt of title compound as yellow crystals in 44 % yield. ¹H-NMR (DMSO-d₆): δ 8.10 (d, 2H), 7.64-7.58 (m, 4H), 7.05 (d, 2H), 6.65 (d, 2H), 6.58 (d, 2H), 6.38 (s, br, 1H), 3.85 (s, 3H), 2.70 (t, 2H), 2.39 (s, 6H).

40

B008 : (E)-3-(4-Chloro-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

General Procedure I gave the oxalate salt of title compound as yellow crystals in 36 %

- 5 yield. ¹H-NMR (DMSO-d₆): δ 8.07 (d, 2H), 7.97-7.87 (m, 3H), 7.63 (d, 1H), 7.51 (d, 2H), 6.84 (d, 2H), 3.74 (t, 2H), 3.48 (t, 2H), 3.05 (s, 3H), 2.70 (s, 6H).

B009 : (E)-3-(3-Bromo-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

- 10 General Procedure I gave the oxalate salt of title compound as yellow crystals in 23 % yield. ¹H-NMR (DMSO-d₆): δ 8.17 (s, 1H), 8.09 (d, 2H), 7.95 (d, 1H), 7.83 (d, 1H), 7.65-7.55 (m, 2H), 7.40 (t, 1H), 6.85 (d, 2H), 3.80 (t, 2H), 3.15 (t, 2H), 3.06 (s, 3H), 2.75 (s, 6H).

15 **B010 : (E)-4-(3-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-oxo-propenyl)-benzonitrile**

General Procedure I gave the oxalate salt of title compound as yellow crystals in 25 % yield. ¹H-NMR (DMSO-d₆): δ 8.12-8.03 (m, 4H), 8.02-7.96 (m, 1H), 7.95-7.88 (m, 2H), 7.67 (d, 1H), 6.85 (d, 2H), 3.75 (t, 2H), 3.10-3.02 (m, 5H), 2.70 (s, 6H).

20

B011: (E)-3-(2,5-Dimethoxy-phenyl)-1-[4-(3-dimethylamino-propylamino)-phenyl]-propenone

General Procedure I gave the oxalate salt of title compound as yellow crystals in 26 % yield. ¹H-NMR (DMSO-d₆): δ 7.98 (d, 2H), 7.92 (d, 1H), 7.83 (d, 1H), 7.49 (d, 1H), 7.06-

- 25 6.97 (m, 2H), 6.75 (s, br, 1H), 6.66 (d, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 3.20 (t, 2H), 3.09 (t, 2H), 2.74 (s, 6H), 1.92 (m, 2H).

B012: (E)-3-(2,4-Dichloro-phenyl)-1-[4-(3-dimethylamino-propylamino)-phenyl]-propenone

- 30 General Procedure I gave the oxalate salt of title compound as yellow crystals in 26 % yield. ¹H-NMR (DMSO-d₆): δ 8.22 (d, 1H), 8.06-7.92 (m, 3H), 7.86 (d, 1H), 7.72 (d, 1H), 7.52 (dd, 1H), 6.88 (s, br, 1H), 6.67 (d, 2H), 3.22 (t, 2H), 3.10 (t, 2H), 2.74 (s, 6H), 1.93 (m, 2H).

35 **B013: (E)-3-[4-(2-Dimethylamino-ethylamino)-phenyl]-1-(2,3,4-trimethoxy-phenyl)-propenone**

General Procedure I gave the fumarate salt of title compound as yellow crystals in 50 % yield. ¹H-NMR (DMSO-d₆): δ 7.48 (d, 2H), 7.42 (d, 1H), 7.29 (d, 1H), 7.12 (d, 1H), 6.90 (d, 1H), 6.64 (d, 2H), 6.58 (s, 2H), 6.52 (s, br, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.77 (s,

- 40 3H), 3.34 (t, 2H), 2.90-2.80 (m, 2H), 2.51 (s, 6H).

B014: (E)-3-[4-(2-Dimethylamino-ethylamino)-phenyl]-1-(2-fluoro-4-methoxy-phenyl)-propenone

General Procedure I gave the fumarate salt of title compound as yellow crystals in 51 % yield. ¹H-NMR (DMSO-d₆): δ 7.78 (t, 1H), 7.58-7.48 (m, 3H), 7.16 (dd, 1H), 6.97-6.87 (m, 2H), 6.64 (d, 2H), 6.58 (s, 2H), 6.41 (s, br, 1H), 3.85 (s, 3H), 3.25 (m, 2H), 2.64 (t, 2H), 2.35 (s, 6H).

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B015: (E)-3-(2,4-Dichloro-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

General Procedure I gave the oxalate salt of title compound as yellow crystals in 39 % yield. ¹H-NMR (DMSO-d₆): δ 8.24 (d, 1H), 7.95 (s, 2H), 7.77 (d, 1H), 7.58-7.50 (m, 2H),

10 7.44-7.34 (m, 2H), 7.12 (dd, 1H), 3.75 (t, 2H), 3.16 (t, 2H), 3.00 (s, 3H), 2.79 (s, 6H).

B016: (E)-3-(4-Chloro-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

General Procedure I gave the oxalate salt of title compound as yellow crystals in 41 %

15 yield. ¹H-NMR (DMSO-d₆): δ 7.94-7.87 (m, 3H), 7.70 (d, 1H), 7.54-7.48 (m, 3H), 7.42-7.34 (m, 2H), 7.11 (dd, 1H), 3.76 (t, 2H), 3.18 (t, 2H), 3.00 (s, 3H), 2.80 (s, 6H).

B017: (E)-3-(2,5-Difluoro-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

20 General Procedure I gave the oxalate salt of title compound as yellow crystals in 15 % yield. ¹H-NMR (DMSO-d₆): δ 8.10-8.04 (m, 1H), 8.00 (d, 1H), 7.75 (d, 1H), 7.53 (d, 1H), 7.44-7.33 (m, 4H), 7.13 (dd, 1H), 3.75 (t, 2H), 3.17 (t, 2H), 3.00 (s, 3H), 2.78 (s, 6H).

B018: (E)-3-(4-Bromo-2-fluoro-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

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General Procedure I gave the oxalate salt of title compound as yellow crystals in 35 % yield. ¹H-NMR (DMSO-d₆): δ 8.09 (t, 1H), 7.96 (d, 1H), 7.73 (d, 1H), 7.69 (dd, 1H), 7.54 (dd, 1H), 7.49 (d, 1H), 7.40 (t, 1H), 7.34 (s, br, 1H), 7.12 (dd, 1H), 3.75 (t, 2H), 3.16 (t, 2H), 3.00 (s, 3H), 2.78 (s, 6H).

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B019: (E)-3-(2-Chloro-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

General Procedure I gave the oxalate salt of title compound as yellow crystals in 27 % yield. ¹H-NMR (DMSO-d₆): δ 8.19 (dd, 1H), 8.02 (d, 1H), 7.92 (d, 1H), 7.57 (dd, 1H),

35 7.53-7.34 (m, 5H), 7.12 (dd, 1H), 3.75 (t, 2H), 3.15 (t, 2H), 3.00 (s, 3H), 2.78 (s, 6H).

B020: (E)-1-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(4-methoxy-phenyl)-propenone

General Procedure I gave the oxalate salt of title compound as yellow crystals in 14 %

40 yield. ¹H-NMR (DMSO-d₆): δ 7.84 (d, 2H), 7.73 (d, 1H), 7.68 (d, 1H), 7.47 (d, 1H), 7.38 (t, 1H), 7.33 (s, br, 1H), 7.08 (dd, 1H), 7.01 (d, 2H), 3.82 (s, 3H), 3.74 (t, 2H), 3.14 (t, 2H), 2.99 (s, 3H), 2.76 (s, 6H).

B021: (E)-3-(2,4-Dimethoxy-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

General Procedure I gave the oxalate salt of title compound as yellow crystals in 55 % yield. ¹H-NMR (DMSO-d₆): δ 7.95 (d, 1H), 7.88 (d, 1H), 7.67 (d, 1H), 7.44-7.32 (m, 2H),

- 5 7.30 (s, br, 1H), 7.06 (dd, 1H), 6.66-6.58 (m, 2H), 3.58 (s, 3H), 3.65 (s, 3H), 3.54 (t, 2H), 3.12 (t, 2H), 2.97 (s, 3H), 2.75 (s, 6H).

B022: (E)-3-(2,4-Dichloro-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone

- 10 General Procedure I gave the fumarate salt of title compound as yellow crystals in 34 % yield. ¹H-NMR (DMSO-d₆): δ 8.20 (d, 1H), 8.05-7.91 (m, 3H), 7.86 (d, 1H), 7.71 (d, 1H), 7.50 (dd, 1H), 6.88 (s, br, 1H), 6.67 (d, 2H), 3.80 (t, 2H), 3.15 (t, 2H), 3.06 (s, 3H), 2.75 (s, 6H).

B023: (E)-1-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(4-methoxy-phenyl)-propenone

General Procedure I gave the oxalate salt of title compound as yellow crystals in 27 % yield. ¹H-NMR (DMSO-d₆): δ 7.72 (d, 2H), 7.54-7.38 (m, 3H), 7.25 (d, 1H), 7.19 (d, 1H), 7.08 (t, 1H), 7.00 (d, 2H), 3.82 (s, 3H), 3.38 (t, 2H), 3.18 (t, 2H), 2.73 (s, 6H), 2.70 (s,

- 20 3H).

B024: (E)-1-(2,3-Dichloro-phenyl)-3-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone

General Procedure I gave the fumarate salt of title compound as yellow crystals in 27 %

- 25 yield. ¹H-NMR (DMSO-d₆): δ 7.76 (dd, 1H), 7.52-7.40 (m, 4H), 7.21 (d, 1H), 6.85 (d, 1H), 6.62 (d, 2H), 6.70 (s, 2H), 3.30-3.22 (m, 2H), 2.65 (t, 2H), 2.35 (s, 6H).

B025: (E)-3-(4-Chloro-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone

- 30 General Procedure I gave the fumarate salt of title compound as yellow crystals in 28 % yield. ¹H-NMR (DMSO-d₆): δ 7.90 (d, 2H), 7.86 (d, 1H), 7.80 (d, 2H), 7.68 (d, 1H), 7.51 (d, 2H), 6.70 (d, 2H), 6.56 (s, 2H), 3.28 (t, 2H), 2.74 (t, 2H), 2.41 (s, 6H).

B026: (E)-3-(2,4-Dimethoxy-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone

- 35 General Procedure I gave the oxalate salt of title compound as yellow crystals in 48 % yield. ¹H-NMR (DMSO-d₆): δ 7.98 (d, 2H), 7.86 (d, 1H), 7.80 (d, 1H), 7.73 (d, 1H), 7.71 (d, 1H), 7.50 (s, 1H), 6.88 (s, br, 1H), 6.68 (d, 2H), 3.90 (s, 3H), 3.85 (s, 3H), 3.50 (t, 2H), 3.20 (t, 2H), 2.80 (s, 6H).

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B027: (E)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(4-methoxy-phenyl)-propenone

General Procedure I gave the fumarate salt of title compound as yellow crystals in 45 % yield. ¹H-NMR (DMSO-d₆): δ 7.98 (d, 2H), 7.86 (d, 1H), 7.82 (d, 2H), 7.73 (d, 1H), 7.00

(d, 2H), 6.88 (s, br, 1H), 6.68 (d, 2H), 6.55 (s, 2H), 3.82 (s, 3H), 3.26 (t, 2H), 2.70 (t, 2H), 2.40 (s, 6H).

B028: (E)-3-(2,5-Dimethoxy-phenyl)-1-[2-(2-dimethylamino-ethylamino)-phenyl]-propenone

General Procedure I gave the oxalate salt of title compound as orange crystals in 61 % yield. ¹H-NMR (DMSO-d₆): δ 9.11 (t, 1H), 8.20 (d, 1H), 7.95 (s, 2H), 7.52 (d, 1H), 7.47 (t, 1H), 7.08-6.95 (m, 2H), 6.90 (d, 1H), 6.71 (t, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.70-3.55 (m, 2H), 3.20 (t, 2H), 2.76 (s, 6H).

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B029: (E)-3-(2,4-Dichloro-phenyl)-1-[2-(2-dimethylamino-ethylamino)-phenyl]-propenone

General Procedure I gave the oxalate salt of title compound as yellow crystals in 69 % yield. ¹H-NMR (DMSO-d₆): δ 9.13 (t, 1H), 8.24 (t, 2H), 8.08 (d, 1H), 7.90 (d, 1H), 7.72 (d, 1H), 7.56-7.40 (m, 2H), 6.93 (d, 1H), 6.70 (t, 1H), 3.70-3.58 (m, 2H), 3.20 (t, 2H), 2.75 (s, 6H).

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B030: (E)-1-[4-(3-Dimethylamino-propylamino)-phenyl]-3-(4-fluoro-phenyl)-propenone

General Procedure I gave the oxalate salt of title compound as yellow crystals in 64 % yield. ¹H-NMR (DMSO-d₆): δ 7.99 (d, 2H), 7.93 (dd, 2H), 7.84 (d, 1H), 7.62 (d, 1H), 7.28 (t, 2H), 6.79 (s, br, 1H), 6.66 (d, 2H), 3.20 (t, 2H), 3.13-3.05 (m, 2H), 2.74 (s, 6H), 2.00-1.85 (m, 2H).

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B031: (E)-3-(2,5-Dimethoxy-phenyl)-1-[2-(3-dimethylamino-propylamino)-phenyl]-propenone

General Procedure I gave the oxalate salt of title compound as orange crystals in 71 % yield. ¹H-NMR (DMSO-d₆): δ 9.15 (t, br, 1H), 8.20 (d, 1H), 7.96 (s, 2H), 7.52 (d, 1H), 7.43 (t, 1H), 7.09-6.95 (m, 2H), 6.85 (d, 1H), 6.68 (t, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.31 (t, 2H), 3.18-3.01 (m, 2H), 2.74 (s, 6H), 2.05-1.90 (m, 2H).

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B032: (E)-3-(2,5-Dimethoxy-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methylamino]-phenyl}-propenone

General Procedure I gave the oxalate salt of title compound as yellow crystals in 44 % yield. ¹H-NMR (DMSO-d₆): δ 7.98 (d, 1H), 7.82 (d, 1H), 7.50 (d, 1H), 7.43-7.30 (m, 2H), 7.27 (t, 1H), 7.08-7.02 (m, 2H), 6.97 (dd, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 3.48 (t, 2H), 2.96 (s, 3H), 2.38 (t, 2H), 2.18 (s, 6H).

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B033: (E)-3-(3-Dibutylamino-phenyl)-1-[2-(3-dimethylamino-propylamino)-phenyl]-propenone

General Procedure I gave the title compound as a orange oil in 40 % yield. ¹H-NMR (DMSO-d₆): δ 9.14 (t, 1H), 8.11 (dd, 1H), 7.84 (d, 1H), 7.59 (d, 1H), 7.40 (t, 1H), 7.20 (t, 1H), 7.07 (d, 1H), 6.95 (s, 1H), 6.80 (d, 1H), 6.68 (dd, 1H), 6.62 (t, 1H), 3.35-3.20 (m,

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6H), 2.32 (t, 2H), 2.15 (s, 6H), 1.80-1.68 (m, 2H), 1.57-1.43 (m, 4H), 1.41-1.25 (m, 4H), 0.92 (t, 6H).

B034: (E)-1-[2-(3-Dimethylamino-propylamino)-phenyl]-3-(3-dipropylamino-phenyl)-propenone

General Procedure I gave the title compound as a red oil in 55 % yield. ¹H-NMR (DMSO-d₆): δ 9.14 (t, 1H), 8.13 (dd, 1H), 7.85 (d, 1H), 7.60 (d, 1H), 7.40 (t, 1H), 7.20 (t, 1H), 7.08 (d, 1H), 6.97 (s, 1H), 6.80 (d, 1H), 6.68 (dd, 1H), 6.62 (t, 1H), 3.35-3.20 (m, 6H), 2.32 (t, 2H), 2.14 (s, 6H), 1.80-1.68 (m, 2H), 1.61-1.45 (m, 4H), 0.90 (t, 6H).

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B035: (E)-1-[2-(2-Dimethylamino-ethylamino)-phenyl]-3-(3-dipropylamino-phenyl)-propenone

General Procedure I gave the title compound as red oil in 54 % yield.

¹H-NMR (DMSO-d₆): δ 9.20 (t, 1H), 8.13 (dd, 1H), 7.85 (d, 1H), 7.62 (d, 1H), 7.42 (t, 1H), 7.20 (t, 1H), 7.10 (d, 1H), 6.97 (s, 1H), 6.79 (d, 1H), 6.68 (dd, 1H), 6.63 (t, 1H), 3.35-3.20 (m, 6H), 2.52 (t, 2H), 2.20 (s, 6H), 1.62-1.45 (m, 4H), 0.90 (t, 6H).

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B036: (E)-3-(2,4-Dimethoxy-phenyl)-1-[2-(3-dimethylamino-propylamino)-phenyl]-propenone

General Procedure I gave the fumarate salt of title compound as yellow crystals in 43 % yield. ¹H-NMR (DMSO-d₆): δ 9.12 (s, br, 1H), 8.11 (dd, 1H), 7.98-7.75 (m, 3H), 7.40 (td, 1H), 6.81 (d, 1H), 6.70-6.57 (m, 3H), 6.53 (s, 2H), 3.90 (s, 3H), 3.84 (s, 3H), 3.28 (t, 2H), 2.77 (t, 2H), 2.48 (s, 6H), 1.95-1.80 (m, 2H).

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B037: (E)-3-(2,4-Dimethoxy-phenyl)-1-[2-(2-dimethylamino-ethylamino)-phenyl]-propenone

General Procedure I gave the fumarate salt of title compound as yellow crystals in 58 % yield. ¹H-NMR (DMSO-d₆): δ 9.13 (t, 1H), 8.10 (dd, 1H), 7.96-7.86 (m, 2H), 7.79 (d, 1H), 7.41 (td, 1H), 6.82 (d, 1H), 6.69-6.60 (m, 3H), 6.58 (s, 2H), 3.90 (s, 3H), 3.85 (s, 3H), 3.40-3.30 (m, 2H), 2.82 (t, 2H), 2.38 (s, 6H).

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B038: (E)-3-(5-Dibutylamino-2-methoxy-phenyl)-1-[2-(2-dimethylamino-ethylamino)-phenyl]-propenone

General Procedure I gave the title compound as a red oil in 63 % yield. ¹H-NMR (DMSO-d₆): δ 9.15 (t, 1H), 8.04 (dd, 1H), 7.92 (d, 1H), 7.82 (d, 1H), 7.41 (t, 1H), 7.10 (d, 1H), 6.96 (d, 1H), 6.82-6.72 (m, 2H), 6.63 (t, 1H), 3.80 (s, 3H), 3.30-3.18 (m, 6H), 2.53 (t, 2H), 2.21 (s, 6H), 1.55-1.40 (m, 4H), 1.49-1.23 (m, 4H), 0.91 (t, 6H).

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B039: (E)-3-(2,4-Dichloro-phenyl)-1-[3-(2-dimethylamino-ethylamino)-phenyl]-propenone

General Procedure I gave the fumarate salt of title compound as yellow crystals in 56 % yield. ¹H-NMR (DMSO-d₆): δ 8.21 (d, 1H), 7.91 (s, 2H), 7.75 (d, 1H), 7.54 (dd, 1H), 7.38 (d, 1H), 7.31-7.20 (m, 2H), 6.90 (d, 1H), 6.58 (s, 2H), 5.70 (t, 1H), 3.20-3.10 (m, 2H), 2.45 (t, 2H), 2.18 (s, 6H).

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B040: (E)-3-[5-(1,1-Dimethyl-allyl)-2-methoxy-phenyl]-1-[4-(3-dimethylamino-propylamino)-phenyl]-propenone

General Procedure I gave the fumarate salt of title compound as yellow crystals in 45 %
5 yield. ¹H-NMR (DMSO-d₆): δ 8.00-7.82 (m, 3H), 7.79 (d, 2H), 7.33 (d, 1H), 7.01 (d, 1H),
6.75 (s, br, 1H), 6.65 (d, 2H), 6.57 (s, 2H), 6.08 (dd, 1H), 5.10-4.94 (m, 2H), 3.85 (s,
3H), 3.18 (t, 2H), 2.65 (t, 2H), 2.39 (s, 6H), 1.88-1.66 (m, 2H), 1.39 (s, 6H).

B041: (E)-3-(3-Dibutylamino-phenyl)-1-[2-(2-dimethylamino-ethylamino)-phenyl]-propenone

General Procedure I gave the title compound as an orange oil in 54 % yield. ¹H-NMR
(DMSO-d₆): δ 9.20 (t, 1H), 8.10 (dd, 1H), 7.83 (d, 1H), 7.61 (d, 1H), 7.40 (t, 1H), 7.19 (t,
1H), 7.08 (d, 1H), 6.95 (s, 1H), 6.78 (d, 1H), 6.70-6.56 (m, 2H), 3.35-3.18 (m, 6H), 2.50
(t, 2H), 2.20 (s, 6H), 1.58-1.41 (m, 4H), 1.40-1.25 (m, 4H), 0.92 (t, 6H).

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B042: (E)-3-(2,4-Dimethoxy-phenyl)-1-[3-(2-dimethylamino-ethylamino)-phenyl]-propenone

General Procedure I gave the oxalate salt of title compound as yellow crystals in 43 %
yield. ¹H-NMR (DMSO-d₆): δ 7.95 (d, 1H), 7.87 (d, 1H), 7.66 (d, 1H), 7.40-7.20 (m, 3H),
20 6.90 (d, 1H), 6.68-6.59 (m, 2H), 3.90 (s, 3H), 3.85 (s, 3H), 3.47 (t, 2H), 3.21 (t, 2H),
2.79 (s, 6H).

B043: (E)-3-(2,5-Dimethoxy-phenyl)-1-[3-(2-dimethylamino-ethylamino)-phenyl]-propenone

General Procedure I gave the oxalate salt of title compound as yellow crystals in 27 %
yield. ¹H-NMR (DMSO-d₆): δ 7.73 (d, 1H), 7.55 (d, 1H), 7.26 (s, 1H), 7.18 (d, 1H), 7.07 (t,
1H), 7.01 (s, 1H), 6.80 (s, 2H), 6.68 (d, 1H), 3.58 (s, 3H), 3.52 (s, 3H), 3.20 (t, 2H), 2.95
(t, 2H), 2.79 (s, 6H).

B044: (E)-3-(2,4-Dimethoxy-phenyl)-1-{2-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

General Procedure I gave the title compound as yellow oil in 36 % yield. ¹H-NMR (DMSO-
d₆): δ 7.80 (d, 1H), 7.68 (d, 1H), 7.45-7.27 (m, 3H), 7.13 (d, 1H), 6.95 (t, 1H), 6.65-6.57
(m, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 3.12 (t, 2H), 2.74 (s, 3H), 2.35 (t, 2H), 2.06 (s, 6H).

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B045: (E)-3-(2,5-Dimethoxy-phenyl)-1-{2-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

General Procedure I gave the title compound as a red oil in 83 % yield. ¹H-NMR (DMSO-
d₆): δ 7.83 (d, 1H), 7.48-7.36 (m, 3H), 7.27 (d, 1H), 7.15 (1H), 7.06-6.92 (m, 3H), 3.80
40 (s, 3H), 3.73 (s, 3H), 3.11 (t, 2H), 2.74 (s, 3H), 2.36 (t, 2H), 2.06 (s, 6H).

B046: (E)-3-(3,5-Bis-trifluoromethyl-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone

General Procedure I gave the title compound as yellow solid in 36 % yield. ¹H-NMR (DMSO-d₆): δ 8.10 (s, 2H), 7.95 (d, 2H), 7.88 (s, 1H), 7.77 (d, 1H), 7.67 (d, 1H), 6.66 (d, 2H), 5.08 (t, br, 1H), 3.30-3.18 (m, 2H), 2.59 (t, 2H), 2.27 (s, 6H).

5 **B047: (E)-3-(3,5-Dimethoxy-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone**

General Procedure I gave the fumarate salt of title compound as yellow crystals in 32 % yield. ¹H-NMR (DMSO-d₆): δ 7.88 (d, 1H), 7.65 (d, 1H), 7.49 (d, 1H), 7.40-7.26 (m, 2H), 7.10-6.92 (m, 3H), 6.58 (d, 2H), 3.80 (s, 6H), 3.61 (t, 2H), 2.62 (t, 2H), 2.39 (s, 6H).

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B048: (E)-1-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-phenyl-propenone

General Procedure I gave the fumarate salt of title compound as yellow crystals in 28 % yield. ¹H-NMR (DMSO-d₆): δ 7.92-7.83 (m, 3H), 7.72 (d, 1H), 7.50-7.43 (m, 4H), 7.40-7.30 (m, 2H), 7.08-7.02 (dd, 1H), 6.58 (s, 2H), 3.62 (t, 2H), 2.95 (s, 3H), 2.73 (t, 2H), 2.45 (s, 6H).

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B049: (E)-3-(4-Diethylaminomethyl-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

20 General Procedure I gave the title compound as yellow oil in 25 % yield. ¹H-NMR (CDCl₃): δ 7.93 (d, 1H), 7.72 (d, 2H), 7.63 (d, 1H), 7.58-7.41 (m, 5H), 7.40 (s, 2H), 7.10-7.04 (m, 1H), 3.72 (s, 2H), 3.65 (t, 2H), 3.16 (s, 3H), 2.73-2.60 (m, 6H), 2.45 (s, 6H), 1.19 (t, 6H).

25 **B050: (E)-3-(3,5-Dimethoxy-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone**

General Procedure I gave the fumarate salt of title compound as yellow crystals in 50 % yield. ¹H-NMR (DMSO-d₆): δ 8.00 (d, 2H), 7.88 (d, 1H), 7.54 (d, 1H), 7.00 (s, 2H), 6.68 (d, 3H), 6.55 (s, 2H), 3.80 (s, 6H), 3.35-3.20 (m, 2H), 2.65 (t, 2H), 2.35 (s, 3H).

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B051: (E)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-phenyl-propenone

General Procedure I gave the fumarate salt of title compound as yellow crystals in 45 % yield. ¹H-NMR (DMSO-d₆): δ 7.98 (d, 2H), 7.94-7.80 (m, 3H), 7.62 (d, 1H), 7.50-7.38 (m, 3H), 6.75-6.65 (m, 3H), 6.57 (s, 2H), 3.31 (q, 2H), 2.67 (t, 2H), 2.36 (s, 6H).

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B052: (E)-3-(4-Diethylaminomethyl-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone

General Procedure I gave the title compound as yellow oil in 36 % yield. ¹H-NMR (CDCl₃): δ 7.98 (d, 2H), 7.90 (d, 1H), 7.63-7.52 (m, 3H), 7.39 (d, 2H), 6.64 (d, 2H), 4.95 (t, 1H), 3.60 (s, 2H), 3.23 (q, 2H), 2.60-2.48 (m, 6H), 2.29 (s, 6H), 1.06 (t, 6H).

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B053: (E)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(2-fluoro-phenyl)-propenone

General Procedure I gave the fumarate salt of title compound as yellow crystals in 50 % yield. ¹H-NMR (DMSO-d₆): δ 8.08 (t, 1H), 8.02-7.88 (m, 3H), 7.74 (d, 1H), 7.54-7.43 (m, 1H), 7.37-7.25 (m, 2H), 6.76 (t, 1H), 6.68 (d, 2H), 6.57 (s, 2H), 3.32 (q, 2H), 2.66 (t, 2H), 2.35 (s, 6H).

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B054: (E)-1-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(2-fluoro-phenyl)-propenone

General Procedure I gave the oxalate salt of title compound as yellow crystals in 26 % yield. ¹H-NMR (DMSO-d₆): δ 8.12 (t, 1H), 7.94 (d, 1H), 7.82 (d, 1H), 7.58-7.47 (m, 2H),
10 7.45-7.28 (m, 4H), 7.13 (dd, 1H), 3.78 (t, 2H), 3.22 (t, 2H), 3.00 (s, 3H), 2.82 (s, 6H).

B055: (E)-3-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2,3,4-trimethoxy-phenyl)-propenone

General Procedure I gave the title compound as yellow oil in 41 % yield.

15 ¹H-NMR (CDCl₃): δ 8.06 (d, 1H), 7.65 (dd, 1H), 7.48 (d, 1H), 7.43 (d, 1H), 7.34 (td, 1H), 7.11 (d, 1H), 7.04 (t, 1H), 6.77 (d, 1H), 3.97 (s, 3H), 3.95 (s, 3H), 3.94 (s, 3H), 3.10 (m, 2H), 2.80 (s, 3H), 2.52 (m, 2H), 2.22 (s, 6H).

B056: (E)-3-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2-methoxy-phenyl)-propenone

20 General Procedure I gave the title compound as yellow oil in 37 % yield. ¹H-NMR (DMSO-d₆): δ 7.73 (d, 1H), 7.69 (dd, 1H), 7.53 (td, 1H), 7.46 (dd, 1H), 7.37 (td, 1H), 7.25 (d, 1H), 7.18 (d, 1H), 7.14 (d, 1H), 7.10-7.01 (m, 2H), 3.84 (s, 3H), 2.95 (t, 2H), 2.70 (s, 3H), 2.33 (t, 2H), 2.05 (s, 6H).

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B057: (E)-3-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2-dimethylaminomethyl-phenyl)-propenone

General Procedure I gave the title compound as yellow oil in 58 % yield. ¹H-NMR (CDCl₃): δ 7.67 (d, 1H), 7.62 (dd, 1H), 7.46-7.30 (m, 5H), 7.13-7.03 (m, 3H), 3.56 (s, 2H), 3.03
30 (t, 2H), 2.71 (s, 3H), 2.35 (t, 2H), 2.17 (s, 12H).

B058: (E)-3-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2-fluoro-4-methoxy-phenyl)-propenone

General Procedure I gave the fumarate salt of title compound as yellow crystals in 41 %
35 yield. ¹H-NMR (DMSO-d₆): δ 7.92 (d, 1H), 7.83 (t, 1H), 7.76 (dd, 1H), 7.47-7.37 (m, 2H), 7.21 (d, 1H), 7.10 (t, 1H), 7.02-6.90 (m, 2H), 6.57 (s, 2H), 3.86 (s, 3H), 3.10 (t, 2H), 2.77-2.61 (m, 5H), 2.29 (s, 6H).

B059: (E)-1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(4-pyridin-2-yl-phenyl)-propenone

40 General Procedure I gave the title compound as a yellow solid in 35 % yield. ¹H-NMR (CDCl₃): δ 8.73 (d, 1H), 8.09-8.02 (m, 4H), 7.87-7.75 (m, 5H), 7.66 (d, 1H), 7.31-7.24 (m, 1H), 6.74 (d, 2H), 3.57 (t, 2H), 3.10 (s, 3H), 2.54 (t, 2H), 2.30 (s, 6H).

B060: (E)-3-(4-Butyl-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

General Procedure I gave the fumarate salt of title compound as yellow crystals in 30 % yield. ¹H-NMR (DMSO-d₆): δ 8.04 (d, 2H), 7.85 (d, 1H), 7.75 (d, 2H), 7.62 (d, 1H), 7.27 (d, 2H), 6.79 (d, 2H), 6.59 (s, 2H), 3.64 (t, 2H), 3.04, (s, 3H), 2.70-2.59 (m, 4H), 2.39 (s, 6H), 1.60-1.55 (m, 2H), 1.35-1.27 (m, 2H), 0.90 (t, 3H).

B061: (E)-1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-quinolin-3-yl-propenone

10 General Procedure I gave the fumarate salt of title compound as yellow crystals in 46 % yield. ¹H-NMR (DMSO-d₆): δ 9.43 (d, 1H), 8.80 (d, 1H), 8.22 (d, 1H), 8.13-8.00 (m, 4H), 7.86-7.78 (m, 2H), 7.67 (dd, 1H), 6.83 (d, 2H), 6.60 (s, 3H), 3.67 (t, 2H), 3.06, (s, 3H), 2.71 (t, 2H), 2.42 (s, 6H).

15 **B062: (E)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(4-pyridin-2-yl-phenyl)-propenone**

General Procedure I gave the fumarate salt of title compound as yellow crystals in 36 % yield. ¹H-NMR (DMSO-d₆): δ 8.70 (d, 1H), 8.18 (d, 2H), 8.08-7.88 (m, 7H), 7.68 (d, 1H), 7.39 (ddd, 1H), 6.69 (d, 1H), 6.65 (t, 1H), 6.57 (s, 1H), 3.28, (q, 2H), 2.58 (t, 2H), 2.29 (s, 6H).

B063: (E)-3-(4-Butyl-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone

General Procedure I gave the fumarate salt of title compound as yellow crystals in 35 % yield. ¹H-NMR (DMSO-d₆): δ 7.83 (d, 2H), 7.69 (d, 1H), 7.61 (d, 2H), 7.46 (d, 1H), 7.13 (d, 2H), 6.54 (d, 2H), 6.48 (d, 1H), 6.43 (s, 1H), 3.12, (q, 2H), 2.51-2.42 (m, 4H), 2.16 (s, 6H), 1.46-1.41 (m, 2H), 1.22-1.14 (m, 2H), 0.77 (t, 3H).

B064: (E)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(4-methoxy-biphenyl-3-yl)-propenone

30 General Procedure I gave the fumarate salt of title compound as yellow crystals in 28 % yield. ¹H-NMR (DMSO-d₆): δ 8.22 (d, 1H), 8.02-7.99 (m, 4H), 7.78-7.74 (m, 2H), 7.71 (d, 1H), 7.48 (dd, 2H), 7.36 (dd, 1H), 7.20 (d, 1H), 6.68 (d, 2H), 6.63 (t, 1H), 6.59 (s, 2H), 3.94 (s, 3H), 3.27, (q, 2H), 2.60 (t, 2H), 2.31 (s, 6H).

35 **B065: (E)-3-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone**

General Procedure I gave the title compound as an orange oil in 33 % yield. ¹H-NMR (CDCl₃): δ 7.44-7.32 (m, 4H), 7.24 (t, 1H), 7.18 (d, 1H), 7.00 (d, 1H), 6.88 (d, 1H), 6.82-6.73 (m, 2H), 3.60 (s, 2H), 3.48 (t, 2H), 2.98 (s, 3H), 2.49 (t, 2H), 2.48-2.34 (br, 8H), 2.30 (s, 6H), 2.20 (s, 3H).

B066: (E)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-quinolin-3-yl-propenone

General Procedure I gave the title compound as yellow solid in 37 % yield. ¹H-NMR (CDCl₃): δ 9.23 (d, 1H), 8.34 (d, 1H), 8.14 (d, 1H), 8.03 (d, 2H), 7.95 (d, 1H), 7.89 (d, 1H), 7.81 (d, 1H), 7.79-7.74 (m, 1H), 7.61 (dd, 1H), 6.67 (d, 2H), 5.04 (t, 1H), 3.26, (dt, 2H), 2.61 (d, 2H), 2.29 (s, 6H).

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B067: (E)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-quinolin-2-yl-propenone

General Procedure I gave the title compound as yellow solid in 17 % yield. ¹H-NMR (CDCl₃): 8.17-8.06 (m, 3H), 8.00 (d, 2H), 7.86 (d, 1H), 7.76 (d, 1H), 7.68 (dd, 1H), 7.59 (d, 1H), 7.49 (dd, 1H), 6.58 (d, 2H), 4.94 (t, 1H), 3.17, (dt, 2H), 2.52 (d, 2H), 2.20 (s, 6H).

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B068: (E)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(4-dimethylamino-phenyl)-propenone

General Procedure I gave the fumarate salt of title compound as yellow crystals in 20 % yield. ¹H-NMR (DMSO-d₆): δ 8.06 (d, 2H), 7.78 (d, 2H), 7.70 (d, 2H), 6.86 (d, 2H), 6.78 (d, 2H), 6.70 (s, 2H), 6.65 (t, 1H), 3.39 (dt, 2H), 3.12 (s, 6H), 2.75 (t, 2H), 2.45 (s, 6H).

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B069: (E)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(4-imidazol-1-yl-phenyl)-propenone

General Procedure I gave the title compound as orange solid in 34 % yield. ¹H-NMR (CDCl₃): δ 7.99 (d, 2H), 7.93 (t, 1H), 7.83-7.75 (m, 3H), 7.60 (d, 1H), 7.47 (d, 2H), 7.34 (t, 1H), 7.25 (t, 1H), 6.66 (d, 2H), 5.01 (t, 1H), 3.25, (dt, 2H), 2.60 (d, 2H), 2.29 (s, 6H).

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B070: (E)-3-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone

General Procedure I gave the fumarate salt of title compound as yellow crystals in 13 % yield. ¹H-NMR (DMSO-d₆): δ 7.97 (d, 2H), 7.74 (d, 1H), 7.52 (d, 1H), 7.43 (d, 1H), 7.31 (dd, 1H), 6.90 (d, 1H), 6.70-6.65 (m, 3H), 6.58 (s, 2H), 4.29 (bs, 4H), 3.34 (dt, 2H), 2.75 (t, 2H), 2.42 (s, 6H).

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B071: (E)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

General Procedure I gave the fumarate salt of title compound as yellow crystals in 15 % yield. ¹H-NMR (DMSO-d₆): δ 7.97 (d, 2H), 7.80 (d, 1H), 7.57 (d, 1H), 7.23 (dd, 1H), 7.12-7.09 (m, 2H), 6.77 (dd, 1H), 6.68 (d, 2H), 6.62 (t, 1H), 6.57 (s, 2H), 3.54 (t, 1H), 3.28 (dt, 2H), 2.96 (s, 3H), 2.62-2.57 (m, 4H), 2.30 (s, 6H), 2.09 (s, 6H).

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B072: (E)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(2-dimethylaminomethyl-phenyl)-propenone

General Procedure I gave the title compound as yellow solid in 10 % yield. ¹H-NMR (CDCl₃): δ 8.24 (d, 1H), 8.00 (d, 2H), 7.76-7.73 (m, 1H), 7.70 (d, 1H), 7.37-7.32 (m, 3H), 6.65 (d, 1H), 4.95 (t, 1H), 3.57 (s, 2H), 3.25 (dt, 2H), 2.60 (t, 2H), 2.29 (s, 6H), 2.28 (s, 6H).

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B073: (E)-1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(4-methoxy-biphenyl-3-yl)-propenone

General Procedure I gave the fumarate salt of title compound as yellow crystals in 36 %
5 yield. ¹H-NMR (DMSO-d₆): δ 8.23 (d, 1H), 8.07 (d, 2H), 8.02 (s, 2H), 7.78-7.71 (m, 3H), 7.48 (dd, 2H), 7.35 (d, 1H), 7.20 (d, 1H), 6.80 (d, 1H), 6.59 (s, 2H), 3.94 (s, 3H), 3.65 (t, 1H), 3.04, (s, 3H), 2.69 (t, 2H), 2.40 (s, 6H).

B074: (E)-3-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2-dimethylaminomethyl-phenyl)-propenone

General Procedure I gave the fumarate salt of title compound as yellow crystals in 42 %
10 yield. ¹H-NMR (DMSO-d₆): δ 7.54-7.38 (m, 4H), 7.27 (s, 2H), 7.22 (t, 1H), 7.05-6.98 (m, 2H), 6.81 (dd, 1H), 6.58 (s, 4H), 3.61 (s, 2H), 3.59 (t, 2H), 2.93 (s, 3H), 2.78 (t, 2H), 2.48 (s, 6H), 2.13 (s, 6H).

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B075: 1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(2-dimethylaminomethyl-phenyl)-propenone

General Procedure I gave the fumarate salt of title compound as orange crystals in 38 %
yield. ¹H-NMR (DMSO-d₆): δ 7.6-7.4 (m, 6H), 7.26 (d, 1H), 7.17 (d, 1H), 6.74 (d, 2H),
20 6.58 (s, 4H), 3.65 (s, 2H), 3.59 (t, 2H), 2.98 (s, 3H), 2.67 (t, 2H), 2.40 (s, 6H), 2.19 (s, 6H).

B076: (E)-3-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

General Procedure I gave the fumarate salt of title compound as yellow crystals in 59 %
25 yield. ¹H-NMR (DMSO-d₆): δ 7.78 (dd, 1H), 7.54 (d, 1H), 7.50-7.33 (m, 5H), 7.18 (d, 1H), 7.14-7.05 (m, 2H), 6.57 (s, 4H), 3.55 (s, 2H), 3.04 (t, 2H), 2.63 (s, 3H), 2.54 (t, 2H), 2.42-2.25 (br, 8H), 2.24 (s, 6H), 2.18 (s, 3H).

B077: (E)-1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(2-dimethylaminomethyl-phenyl)-propenone

General Procedure I gave the title compound as yellow oil in 33% yield. ¹H-NMR (CDCl₃): δ
30 8.23 (d, 1H), 8.01 (d, 2H), 7.74-7.71 (m, 1H), 7.50 (d, 1H), 7.35-7.29 (m, 3H), 6.70 (d, 1H), 3.57-3.52 (m, 4H), 3.07 (s, 3H), 2.51 (t, 2H), 2.30 (s, 6H), 2.26 (s, 6H).

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B078: (E)-1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(4-imidazol-1-yl-phenyl)-propenone

General Procedure I gave the title compound as pale brown solid in 23 % yield. ¹H-NMR
(CDCl₃): δ 8.00 (d, 2H), 7.90 (t, 1H), 7.77 (d, 1H), 7.73 (d, 2H), 7.59 (d, 1H), 7.42 (d,
40 2H), 7.31 (t, 1H), 7.22 (t, 1H), 6.71 (d, 2H), 3.54 (t, 2H), 3.07, (s, 3H), 2.47 (t, 2H), 2.29 (s, 6H).

B079: (E)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(4-phenoxy-phenyl)-propenone

General Procedure I gave the title compound as yellow crystals in 39 % yield. ¹H-NMR (CDCl₃): δ 7.98 (d, 2H), 7.78 (d, 1H), 7.63 (d, 2H), 7.51 (d, 1H), 7.42 (dd, 2), 7.18 (dd, 1H), 7.10-7.01 (m, 4H), 4.96 (t, 1H), 3.24 (dt, 2H) 2.60 (t, 2H), 2.29 (s, 6H).

5 **B080: (E)-3-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2-dimethylaminomethyl-phenyl)-propenone**

General Procedure I gave the title compound as a green oil in 58 % yield. ¹H-NMR (CDCl₃): δ 7.66 (d, 1H), 7.60 (dd, 1H), 7.43 (m, 3H), 7.35 (m, 2H), 7.11 (d, 1H), 7.06 (d, 1H), 7.03 (d, 1H), 3.56 (s, 2H), 3.05 (t, 2H), 2.71 (s, 3H), 2.36 (t, 2H), 2.17 (s, 12H).

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B081: (E)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(3-phenoxy-phenyl)-propenone

General Procedure I gave the fumarate salt of title compound as yellow crystals in 29 % yield. ¹H-NMR (DMSO-d₆): δ 7.78 (d, 2H), 7.70 (d, 1H), 7.43-7.37 (m, 3H), 7.27-7.17 (m, 15 H), 6.95 (dt, 1H), 6.86-6.80 (m, 3H), 6.49-6.42 (m, 3H), 6.37 (s, 1H), 3.07 (q, 2H), 2.38 (t, 2H), 2.09 (s, 6H).

B082: (E)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(3-morpholin-4-ylmethyl-phenyl)-propenone

20 General Procedure I gave the fumarate salt of title compound as yellow crystals in 37 % yield. ¹H-NMR (DMSO-d₆): δ 7.99 (d, 2H), 7.88 (d, 1H), 7.75-7.72 (m, 2H), 7.61 (d, 1H), 7.43-7.36 (m, 2H), 6.74-6.71 (m, 3H), 6.57 (s, 1H), 3.58 (t, 2H), 3.51 (s, 2H), 3.31 (q, 2H), 2.67 (t, 2H), 2.39-2.36 (m, 10H).

25 **B083: (E)-1-(2-Fluoro-4-methoxy-phenyl)-3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone**

General Procedure J gave the fumarate salt of title compound as yellow crystals in 33 % yield. ¹H-NMR (DMSO-d₆): δ 7.76 (dd, 1H), 7.65 (t, 1H), 7.67 (d, 1H), 7.37 (dd, 1H), 7.29 (dd, 1H), 7.20-7.15 (m, 2H), 7.02-6.75 (m, 5H), 6.44 (s, 3H), 3.70 (s, 3H), 3.61 (s, 30 3H), 2.81 (t, 4H), 2.45 (bs, 4H), 2.17 (s, 3H).

B084: (E)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

General Procedure I gave the fumarate salt of title compound as yellow crystals in 11 % yield. ¹H-NMR (DMSO-d₆): δ 7.93 (d, 1H), 7.85-7.81 (m, 3H), 7.58 (d, 1H), 7.25-7.21 (m, 35 3H), 6.63 (bs, 1H), 6.55 (d, 2H), 6.45 (s, 5H), 3.47 (s, 2H), 3.22 (q, 2H), 2.66 (t, 2H), 2.45 (bs, 2H), 2.32 (s, 6H), 2.20 (s, 3H).

40 **B085: (E)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-[3-(pyridin-3-ylamino)-phenyl]-propenone**

General Procedure I gave the fumarate salt of title compound as brown-orange crystals in 6 % yield. ¹H-NMR (DMSO-d₆): δ 8.61 (bs, 1H), 8.53 (d, 1H), 8.21 (dd, 1H), 8.10 (dd, 2), 7.95 (d, 1H), 7.72 (d, 1H), 7.66 (dd, 1H), 7.61 (t, 1H), 7.56 (dt, 1H), 7.49 (t, 1H), 7.41

(dd, 1H), 7.30 (dd, 1H), 6.82 (d, 2H), 6.76-6.73 (m, 2H), 3.41, (q, 2H), 2.70 (t, 2H), 2.42 (s, 6H).

B086: (E)-3-(4-Diethylamino-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

General Procedure I gave the oxalate salt of title compound as yellow crystals in 4 % yield. ¹H-NMR (DMSO-d₆): δ 8.02 (d, 1H), 7.65-7.57 (m, 4H), 6.84 (d, 2H), 6.69 (d, 2H), 3.79 (t, 2H), 4.41 (q, 4H), 3.13 (t, 2H), 3.04 (s, 3H), 2.76 (s, 6H), 1.12 (t, 6H).

B087: (E)-1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-quinolin-2-yl-propenone

General Procedure I gave the title compound as brown oil in 18% yield. ¹H-NMR (CDCl₃): δ 8.24-8.08 (m, 5H), 7.93 (d, 1H), 7.82 (d, 1H), 7.75 (t, 1H), 7.66 (d, 1H), 7.55 (t, 1H), 7.73 (d, 1H), 3.58 (t, 2H), 3.09 (s, 3H), 2.56 (t, 2H), 2.33 (s, 6H).

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B088: (E)-N-{3-[3-(2,5-Dimethoxy-phenyl)-acryloyl]-phenyl}-2-dimethylamino-acetamide

General Procedure I gave the fumarate salt of title compound as yellow crystals in 81 % yield. ¹H-NMR(DMSO-d₆): δ 10.2 (s, 1H), 8.5 (t, 1H), 8.1 (m, 2H), 8.0 (m, 2H), 7.7 (t/s, 2H), 7.2 (bs, 2H), 6.8 (s, 2H), 4.0 (s, 3H), 3.9 (s, 3H), 3.3 (s, 2H), 2.7 (s, 6H).

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B089: (E)-N-{3-[3-(4-Dibutylamino-phenyl)-acryloyl]-phenyl}-2-dimethylamino-acetamide

General Procedure I gave the title compound as yellow oil in 32 % yield. ¹H-NMR(CDCl₃): δ 9.33 (bs, 1H), 8.04 (dd, 1H), 8.00 (t, 1H), 7.81 (d, 1H), 7.74 (dt, 1H), 7.53 (d, 2H), 7.46 (t, 1H), 7.31 (d, 1H), 6.63 (d, 2H), 3.34 (t, 4H), 3.13 (s, 2H), 2.42 (s, 6 H), 1.63 (m, 4H), 1.38 (six., 4H), 0.98 (t, 6H).

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B090: (E)-3-(2,4-Dichlorophenyl)-1-{4-[(2-dimethylamino-ethyl)methylamino]phenyl}-propan-1-one:

General Procedure L gave the fumaric salt of the title compound as yellow crystals in 7% yield. ¹H-NMR(DMSO-d₆): δ 7.82 (d, 2H), 7.57 (d, 1H), 7.43 (d, 1H); 7.35 (dd, 1H), 6.73 (d, 2H), 6.58 (s, 2H), 3.58 (t, 2H), 3.19 (t, 2H), 3.00 (s, 3H), 2.98 (t, 2H), 2.59 (t, 2H), 2.33 (s, 6H).

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B091: (E)-3-[5-Bromo-2-(4-methyl-piperazin-1-yl)-phenyl]-1-(2-fluoro-4-methoxy-phenyl)-propenone

General Procedure I gave the title compound as yellow crystals in 65 % yield. ¹H-NMR (CDCl₃): δ 8.05 (dd, 1H), 7.91 (t, 1H), 7.76 (d, 1H), 7.46 (dd, 1H), 7.41 (dd, 1H), 6.96 (dd, 1H), 6.82 (dd, 1H), 6.69 (dd, 1H), 3.90 (s, 3H), 3.01 (t, 4H), 2.64 (bs, 4H), 2.39 (s, 3H).

40

B092: (E)-3-{3-[4-(2-Methoxy-acetyl)-piperazin-1-yl]-phenyl}-1-(4-methoxy-phenyl)-propenone

General Procedure I gave the title compound as yellow crystals in 8% yield. ¹H-NMR(CDCl₃): δ 8.05 (d, 2H), 7.77 (d, 1H), 7.52 (d, 1H), 7.36 (t, 1H), 7.23 (bd, 1H), 7.16 (bs, 1H), 7.00 (m, 3H), 4.17 (s, 2H), 3.90 (s, 3H), 3.82 (m, 2H), 3.72 (m, 2H), 3.46 (s, 3H), 3.24 (t, 4H)

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B093: (E)-N-{3-[3-(2,4-Dichloro-phenyl)-acryloyl]-phenyl}-2-dimethylamino-acetamide

General Procedure I gave the title compound as yellow oil in 23% yield. ¹H-NMR(CDCl₃): δ 9.37 (s, 1H), 8.15 (m, 2H), 8.01 (dt, 1H), 7.77 (dt, 1H), 7.73 (d, 1H), 7.5 (m, 2H), 7.33 (dd, 1H), 3.14 (s, 2H), 2.43 (s, 6H).

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B094 : (E)-N-{3-[3-(4-Dibutylamino-phenyl)-acryloyl]-phenyl}-2-(4-methyl-piperazin-1-yl)-acetamide

General Procedure I gave the title compound as red oil in 64% yield. ¹H-NMR (DMSO-d₆): δ 9.81 (s, 1H), 8.17(t, 1H), 7.84 (dd, 1H), 7.73 (bd, 1H), 7.6 (m, 3H), 7.4 (m, 2H), 6.62 (d, 2H), 3.30 (m, 4H), 3.07 (s, 2H), 2.44 (m, 4H), 2.32 (m, 4H), 2.11 (s, 3H), 1.49 (m, 4H), 1.29 (six, 4H), 0.86 (t, 6H).

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B095: (E)-1-(3-Dimethylaminomethyl-phenyl)-3-[2'-methoxy-3-(4-methyl-piperazin-1-yl)-biphenyl-4-yl]-propenone

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General Procedure I gave the fumarate salt of title compound as yellow crystals in 27% yield. ¹H-NMR (DMSO-d₆): δ 7.85 (m 3H), 7.77 (d, 1H), 7.64 (d, 1H), 7.40 (bd, 1H), 7.35 (t, 1H), 7.18 (m, 2H), 7.06 (bd, 1H), 7.01 (d, 1H), 6.93 (d, 1H), 6.85 (t, 1H), 6.40 (s, 3H), 3.78 (s, 3H), 3.49 (s, 2H), 2.95 (t, 4H), 2.5 (m, 4H) 2.22 (s, 3H), 2.18 (s, 6H).

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B096: (E)-1-(2-Dimethylaminomethyl-phenyl)-3-[2'-methoxy-3-(4-methyl-piperazin-1-yl)-biphenyl-4-yl]-propenone

General Procedure I gave the fumarate salt of title compound as brown crystals in 61% yield. ¹H-NMR (DMSO-d₆): δ 7.62 (d, 1H), 7.34 (d, 1H), 7.2-7.1 (m, 6H), 7.05-6.75 (m, 5H), 6.39 (s, 4H), 3.56 (s, 3H), 3.35 (s 2H), 3.16 (m, 4H), 2.29 (s, 6H), 2.11 (m, 4H), 1.91 (s, 3H).

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B097: (E)-N-{4-[3-(2,4-Dichloro-phenyl)-acryloyl]-phenyl}-N-(2-dimethylamino-ethyl)-acetamide

General Procedure I gave the title compound as yellow crystals in 12% yield. ¹H-NMR (CDCl₃): δ 8.14 (d, 1H), 8.08 (d, 2H), 7.70 (d, 1H), 7.48 (d, 1H), 7.47 (d, 1H), 7.40 (d, 2H), 7.32 (dd 1H), 3.87 (t, 2H), 2.42 (t, 2H), 2.22 (s, 6H), 1.91 (s, 3H).

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B098: (E)-1-(3-Dimethylaminomethyl-4-hydroxy-phenyl)-3-[2'-methoxy-3-(4-methyl-piperazin-1-yl)-biphenyl-4-yl]-propenone

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General Procedure I gave the title compound as yellow oil in 6% yield. ¹H-NMR (CDCl₃): δ 8.15 (d, 1H), 7.86 (dd, 1H), 7.71 (d, 1H), 7.62 (d, 1H), 7.50 (d, 1H), 7.3-7.1 (m, 4H), 6.95 (m, 2H), 6.81 (d, 1H), 3.78 (s, 3H), 3.68 (s, 2H), 3.00 (t, 4H), 2.61 (bs, 4H), 2.33 (s, 3H), 2.31 (s, 6H).

B099: (E)-1-(2-Dimethylaminomethyl-4-methoxy-phenyl)-3-[6-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone

General Procedure I gave the fumarate salt of title compound as yellow crystals in 27 %
5 yield. ¹H-NMR (DMSO-d₆): δ 7.72-7.59 (m, 5 H), 7.48-7.30 (m, 5H), 7.1 (m, 2H), 7.06 (dd, 1H), 6.60 (4H), 3.85 (s, 3H), 3.72 (s, 2H), 2.84 (bs, 4H), 2.29 (b, 4H), 2.22 (s, 6H), 2.18 (s, 3H).

B100: (E)-1-(3-Dimethylaminomethyl-4-methoxy-phenyl)-3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone

General Procedure I gave the fumarate salt of title compound as yellow crystals in 57 %
10 yield. ¹H-NMR (DMSO-d₆): δ 8.20 (dd, 1H), 8.14 (d, 1H), 8.06 (d, 1H), 7.95 (d, 1H), 7.85 (d, 1H), 7.52 (dd, 1H), 7.38-7.32 (m, 2H), 7.18-7.10 (m, 3H), 7.04 (td, 1H), 6.57 (s, 4H), 3.90 (s, 3H), 3.78 (s, 3H), 3.77 (s, 2H), 3.00 (t, 4H), 2.67 (bs, 4H), 2.38 (s, 6H), 2.36 (s,
15 3H).

B101: (E)-1-[3-(2-Dimethylamino-ethylamino)-phenyl]-3-[3',5'-dimethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone

General Procedure I gave the title compound as yellow crystals in 60% yield. ¹H-NMR
20 (DMSO-d₆): δ 8.02 (d, 2H), 7.66-7.57 (m, 2H), 7.49 (d, 1H), 7.37-7.32 (m, 3H), 7.14 (d, 1H), 7.05 (d, 1H), 6.97-6.92 (m, 2H), 3.83 (s, 3H), 3.50(s, 2H), 2.86 (t, 4H), 2.33 (s, 10H), 2.17 (s, 3H), 2.06 (s, 6H).

B102: (E)-1-(2-Dimethylaminomethyl-4-methoxy-phenyl)-3-[3',5'-dimethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone

General Procedure I gave the compound as yellow oil in 55% yield. ¹H-NMR (DMSO-d₆): δ
25 8.09 (d, 1H), 8.02 (d, 1H), 7.85 (d, 1H), 7.65 (dd, 1H), 7.37-7.24 (m, 5H), 7.18 (d, 1H), 6.98 (bs, 1H), 6.88 (dd, 1H), 5.69 (t, 1H), 3.16 (q, 2H), 2.94 (t, 4H), 2.50 (t, 4H), 2.45 (t, 2H), 2.34 (s, 6H), 2.26 (s, 3H), 2.19 (s, 6H).

30

B103: (E)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-{3-[4-(2-methoxy-acetyl)-piperazin-1-yl]-phenyl}-propenone

General Procedure I gave the fumarate salt of title compound as yellow crystals in 19 %
yield. ¹H-NMR (DMSO-d₆): δ 7.98 (d, 2H); 7.85 (d, 1H); 7.58 (d, 1H); 7.41 (bs, 1H); 7.32-
35 7.24 (m, 2H); 7.02 (dt, 1H); 6.70-6.63 (m, 3H); 6.58 (s, 2H); 4.14 (s, 2H); 3.62-3.56 (m, 4H); 3.31-3.23 (m, 9H), 2.63 (t, 2H), 2.33 (s, 6H).

B104: (E)-3-{3-[4-(2-Dimethylamino-acetyl)-piperazin-1-yl]-phenyl}-1-(3-dimethylaminomethyl-phenyl)-propenone

General Procedure I gave the title compound as yellow oil in 33% yield. ¹H-NMR (DMSO-
40 d₆): δ 8.08 (dt, 1H), 7.99 (bs, 1H), 7.90 (d, 1H), 7.70 (d, 1H), 7.60 (dt, 1H), 7.53 (t, 1H), 7.45 (bs, 1H), 7.33-7.31 (m, 2H), 7.09-7.05 (m, 1H), 3.66 (t, 2H), 3.61 (t, 2H), 3.49 (s, 2H), 3.26-3.20 (m, 4H), 3.12 (s, 2H), 2.19 (s, 6H), 2.17 (s, 6H).

B105: (E)-3-{3-[4-(2-Dimethylamino-acetyl)-piperazin-1-yl]-phenyl}-1-(2-fluoro-4-methoxy-phenyl)-propenone

General Procedure I gave the title compound as yellow oil in 28% yield.

¹H-NMR (DMSO-d₆): δ 7,83 (t, 1H), 7,61 (d, 1H), 7,49 (dd, 1H), 7,35-7,28 (m, 2H), 7,21 (bd, 1H), 7,06 (dd, 1H), 7,00-6,92 (m, 2H), 3,87 (s, 3H), 3,69 (t, 2H), 3,60 (t, 2H), 3,24-3,18 (m, 4H), 3,12 (s, 2H), 2,19 (s, 6H).

B106: (E)-1-(2-Fluoro-4-methoxy-phenyl)-3-[4-(4-methyl-piperazin-1-yl)-biphenyl-2-yl]-propenone

10 General Procedure I gave the title compound as yellow oil in 64% yield.

¹H-NMR (DMSO-d₆): δ 7,77 (t, 1H), 7,57-7,34 (m, 6H), 7,29-7,24 (m, 3H), 7,14 (dd, 1H), 6,97 (d, 1H), 6,91 (td, 1H), 3,85 (s, 3H), 3,27 (t, 4H), 2,50 (t, 4H), 2,24 (s, 3H).

B107: (E)-1-[3-(2-Dimethylamino-ethylamino)-phenyl]-3-[4-(4-methyl-piperazin-1-yl)-biphenyl-2-yl]-propenone

15 General Procedure I gave the fumarate salt of title compound as yellow crystals in 45% yield. ¹H-NMR (DMSO-d₆): δ 7,77 (d, 1H), 7,61 (d, 1H), 7,55 (d, 1H), 7,49-7,34 (m, 4H), 7,30-7,23 (m, 4H), 7,18 (t, 1H), 7,13 (dd, 1H), 6,88 (dd, 1H), 6,58 (s, 4H), 3,32 (t, 4H), 3,26 (t, 2H), 2,73 (t, 2H), 2,57 (t, 4H), 2,41 (s, 6H), 2,30 (s, 1H).

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B108: (E)-1-(4-Hydroxy-phenyl)-3-[4-(4-methyl-piperazin-1-yl)-biphenyl-2-yl]-propenone

General Procedure I gave the title compound as yellow crystals in 23% yield. ¹H-NMR (DMSO-d₆): δ 10,43 (s, 1H), 8,02 (d, 2H), 7,84 (d, 1H), 7,61 (d, 1H), 7,56 (d, 1H), 7,48-7,38 (m, 3H), 7,29-7,23 (m, 3H), 7,11 (dd, 1H), 6,88 (d, 2H), 3,31 (t, 4H), 2,50 (t, 4H), 2,26 (s, 3H).

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B109: (E)-1-(3-Dimethylaminomethyl-phenyl)-3-[4-(4-methyl-piperazin-1-yl)-biphenyl-2-yl]-propenone

30 General Procedure I gave the fumarate salt of title compound as yellow crystals in 31% yield. ¹H-NMR (DMSO-d₆): δ 8,07 (db, 1H), 7,96 (bs, 1H), 7,83 (d, 1H), 7,68-7,52 (m, 4H), 7,48-7,36 (m, 3H), 7,30-7,26 (m, 3H), 7,15 (dd, 1H), 6,58 (s, 1½H), 3,67 (s, 2H), 3,36 (t, 4H), 2,66 (t, 4H), 2,36 (s, 3H), 2,27 (s, 6H).

B110: (E)-1-(3-Dimethylaminomethyl-4-methoxy-phenyl)-3-[4-(4-methyl-piperazin-1-yl)-biphenyl-2-yl]-propenone

General Procedure I gave the title compound as yellow crystals in 10% yield. ¹H-NMR (DMSO-d₆): δ 8,15 (dd, 1H), 7,96 (d, 1H), 7,82 (d, 1H), 7,62 (d, 1H), 7,55 (d, 1H); 7,48-7,38 (m, 3H), 7,30-7,24 (m, 3H), 7,14-7,10 (m, 2H), 3,89 (s, 3H), 3,42 (s, 2H), 3,32 (t, 4H), 2,50 (t, 4H), 2,26 (s, 3H), 2,16 (s, 6H).

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B111: (E)-1-(2-Dimethylaminomethyl-4-methoxy-phenyl)-3-[5-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone

General Procedure I gave the fumarate salt of title compound as yellow/brown crystals in 60% yield. ¹H-NMR (DMSO-d₆): δ 7.79-7.72 (m, 3H), 7.58 (d, 1H), 7.50-7.35 (m, 6H), 7.23 (bs, 1H), 7.12 (d, 1H), 7.01 (dd, 1H), 6.58 (s, 4H), 3.85 (s, 3H), 3.80 (s, 2H), 3.34 (t, 4H), 2.63 (t, 4H), 2.34 (s, 3H), 2.27 (s, 6H).

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B112: (E)-1-[3-(2-Dimethylamino-ethylamino)-phenyl]-3-[5-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone

General Procedure I gave the fumarate salt of title compound as yellow crystals in 50% yield. ¹H-NMR (DMSO-d₆): δ 7.92 (d, 1H), 7.76-7.71 (m, 3H), 7.56-7.36 (m, 6H), 7.32-
10 7.24 (m, 3H), 6.90 (dd, 1H), 6.57 (s, 4H), 3.35-3.31 (m, 6H), 2.84 (t, 2H), 2.62 (t, 4H), 2.49 (s, 6H), 2.33 (s, 3H).

B113: (E)-1-[3-(2-Dimethylamino-ethylamino)-phenyl]-3-{4-[(2-dimethylamino-ethyl)-methyl-amino]-3',5'-dimethyl-biphenyl-3-yl}-propenone

15 General Procedure I gave the fumarate salt of title compound as orange crystals in 61% yield. ¹H-NMR (DMSO-d₆): δ 8.08 (d, 1H), 8.01 (d, 1H), 7.85 (d, 1H), 7.66 (dd, 1H), 7.41 (bd, 1H), 7.34-7.24 (m, 5H), 6.98 (bs, 1H), 6.89 (dd, 1H), 6.55 (s, 4H), 3.32 (t, 2H), 3.16 (t, 2H), 2.83-2.73 (m, 7H), 2.46 (s, 6H), 2.34 (s, 6H), 2.32 (s, 6H).

20 **B114: (E)-3-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-3',5'-dimethyl-biphenyl-3-yl}-1-(2-dimethylaminomethyl-4-methoxy-phenyl)-propenone**

General Procedure I gave the fumarate salt of title compound as orange crystals in 32% yield. ¹H-NMR (DMSO-d₆): δ 8.03 (d, 1H), 7.77-7.72 (m, 2H), 7.65 (dd, 1H), 7.51 (d, 1H), 7.33 (bs, 2H), 7.24 (d, 1H), 7.12 (d, 1H), 7.02-6.98 (m, 2H), 6.56 (s, 4H), 3.84 (s, 3H),
25 3.75 (s, 2H), 3.14 (t, 2H), 2.72-2.67 (m, 5H), 2.34 (s, 6H), 2.32 (s, 6H), 2.24 (s, 6H).

B115: (E)-1-(2-Amino-phenyl)-3-[3',5'-dimethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone

General Procedure I gave the fumarate salt of title compound as yellow crystals in 72%
30 yield. ¹H-NMR (DMSO-d₆): δ 8.15-8.11 (m, 2H), 7.99 (bs, 2H), 7.64 (dd, 1H), 7.39 (bs, 2H), 7.34 (bs, 2H), 7.28 (td, 1H), 7.18 (d, 1H), 6.98 (bs, 1H), 6.80 (d, 1H), 6.59 (td, 1H), 2.95 (t, 4H), 2.35 (s, 6H), 2.27 (d, 3H).

35 **B116: (E)-1-[3-(2-Dimethylamino-ethylamino)-phenyl]-3-(3',5'-dimethyl-4-piperazin-1-yl)-biphenyl-3-yl]-propenone**

General Procedure I gave the BOC-protected analogue of the title compound. Subsequent deprotection using TFA (20 eqv) in methylene chloride afforded the title compound. The product was isolated as the fumaric acid salt as yellow crystals in 7% yield.
40 ¹H-NMR (DMSO-d₆): δ 8.13 (d, 1H), 8.01 (d, 1H), 7.88 (d, 1H), 7.69 (dd, 1H), 7.40-7.21 (m, 6H), 7.00 (bs, 1H), 6.89 (dd, 1H), 6.54 (s, 4H), 3.21 (t, 2H), 3.15 (bd, 4H), 3.00 (bd, 4H), 2.58 (t, 2H), 2.35 (s, 6H), 2.29 (s, 6H).

B117: (E)-1-(2-Dimethylaminomethyl-4-methoxy-phenyl)-3-(3',5'-dimethyl-4-piperazin-1-yl)-biphenyl-3-yl]-propenone

General Procedure I gave the BOC-protected analogue of the title compound. Subsequent deprotection using TFA (20 eqv) in methylene chloride afforded the title compound. The product was isolated as the fumaric acid salt as yellow crystals in 38% yield.

- ¹H-NMR (DMSO-d₆): δ 8.05 (d, 1H), 7.70-7.62 (m, 3H), 7.46 (d, 1H), 7.34 (bs, 2H), 7.20 (d, 1H), 7.10 (d, 1H), 6.99-6.95 (m, 2H), 6.55 (s, 4H), 3.84 (s, 3H), 3.64 (s, 2H), 3.06 (s, 8H), 2.34 (s, 6H), 2.16 (s, 6H).

B118: (E)-3-{3-Bromo-5-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2-dimethylaminomethyl-phenyl)-propenone

- 10 General Procedure I gave the fumarate salt of title compound as yellow crystals in 22% yield. ¹H-NMR (DMSO-d₆): δ 7.49-7.40 (m, 4H), 7.31 (d, 1H), 7.24-7.18 (m, 2H), 7.00 (bs, 1H), 6.85 (t, 1H), 6.59 (s, 4H), 3.59 (s, 2H), 3.53 (t, 2H), 2.92 (s, 3H), 2.60 (t, 2H), 2.35 (s, 6H), 2.09 (s, 6H).

15 **B119: (E)-3-{5-[(2-Dimethylamino-ethyl)-methyl-amino]-2'-methyl-biphenyl-3-yl}-1-(2-dimethylaminomethyl-phenyl)-propenone**

- General Procedure I gave the fumarate salt of title compound as yellow crystals in 93% yield. ¹H-NMR (DMSO-d₆): δ 7.52 (bd, 1H), 7.49-7.38 (m, 3H), 7.34 (bs, 2H), 7.29-7.21 (m, 4H), 7.02-6.98 (m, 2H), 6.68 (bs, 1H), 6.57 (s, 4H), 3.62-3.59 (m, 4H), 2.96 (s, 3H), 2.76 (t, 2H), 2.45 (s, 6H), 2.25 (s, 3H), 2.13 (s, 6H).

B120: (E)-3-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-2'-methyl-biphenyl-4-yl}-1-(2-dimethylaminomethyl-phenyl)-propenone

- General Procedure I gave the fumarate salt of title compound as yellow crystals in 36% yield. ¹H-NMR (DMSO-d₆): δ 7.86 (d, 1H), 7.63 (d, 1H), 7.53-7.42 (m, 4H), 7.29-7.18 (m, 5H); 7.10-7.06 (m, 2H), 6.57 (s, 4H), 3.61 (s, 2H), 3.13 (t, 2H); 2.67-2.63 (m, 6H), 2.30 (s, 6H), 2.26 (s, 3H), 2.14 (s, 6H).

30 **B121: (E)-3-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-2'-methyl-biphenyl-4-yl}-1-(3-dimethylaminomethyl-phenyl)-propenone**

- General Procedure I gave the fumarate salt of title compound as yellow crystals in 49% yield. ¹H-NMR (DMSO-d₆): δ 8.10-8.05 (m, 3H), 8.00 (d, 1H), 7.85 (d, 1H), 7.63 (d, 1H), 7.55 (t, 1H), 7.33-7.26 (m, 4H), 7.14 (bs, 1H), 7.09 (bd, 1H), 6.56 (s, 3H), 3.66 (s, 2H), 3.18 (t, 2H), 2.79-2.74 (m, 5H), 2.32 (s, 6H), 2.29 (s, 3H), 2.27 (s, 6H).

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B122: (E)-3-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-2'-methyl-biphenyl-4-yl}-1-(3-dimethylaminomethyl-4-hydroxy-phenyl)-propenone

- General Procedure I gave the fumarate salt of title compound as orange powder in 18% yield. ¹H-NMR (DMSO-d₆): δ 8.04 (m, 4H), 7.83 (d, 1H), 7.32-7.25 (m, 4H), 7.08 (bs, 1H), 7.04 (dd, 1H), 6.85 (d, 1H), 3.70 (s, 2H), 3.05 (t, 2H), 2.77 (s, 3H), 2.47 (t, 2H), 2.29 (s, 9H), 2.08 (s, 6H).

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B123: (E)-3-[5-Bromo-2-(4-methyl-piperazin-1-yl)-phenyl]-1-(2-dimethylaminomethyl-phenyl)-propenone

General Procedure I gave the fumarate salt of title compound as yellow crystals in 63% yield. ¹H-NMR (DMSO-d₆): δ 7.98 (d, 1H), 7.51 (dd, 1H), 7.47-7.36 (m, 5H), 7.17 (d, 1H), 7.03 (d, 1H), 3.46 (s, 2H), 2.78 (t, 4H), 2.23 (bs, 4H); 2.14 (s, 3H), 2.02 (s, 6H).

5 **B124: (E)-3-[2-Bromo-5-(4-methyl-piperazin-1-yl)-phenyl]-1-(2-dimethylaminomethyl-phenyl)-propenone**

General Procedure I gave the fumarate salt of title compound as yellow crystals in 19% yield. ¹H-NMR (DMSO-d₆): δ 7.56-7.43 (m, 7H), 7.38 (d, 1H), 6.97 (dd, 1H), 6.60 (s, 1H), 3.65 (s, 2H), 3.26 (t, 4H), 2.57 (t, 4H), 2.31 (s, 3H), 2.13 (s, 6H).

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B125: (E)-3-{5-[(2-Dimethylamino-ethyl)-methyl-amino]-2'-methyl-biphenyl-3-yl}-1-(2-dimethylaminomethyl-4-methoxy-phenyl)-propenone

General Procedure I gave the title compound as yellow oil in 36% yield. ¹H-NMR (DMSO-d₆): δ 7.55 (d, 1H), 7.33 (d, 2H), 7.29-7.21 (m, 4H), 7.04 (d, 1H), 6.97-6.94 (m, 2H),
15 6.91 (dd, 1H), 6.62 (bs, 1H), 3.81 (s, 3H), 3.56 (s, 2H), 3.47 (t, 2H), 2.96 (s, 3H), 2.39 (t, 2H), 2.25 (s, 3H), 2.17 (s, 6H), 2.07 (s, 6H).

B126: (E)-3-[3-Bromo-5-(3-dimethylamino-propylamino)-phenyl]-1-(2-dimethylaminomethyl-phenyl)-propenone

20 General Procedure I gave the title compound as green/yellow oil in 28% yield.

¹H-NMR (DMSO-d₆): δ 7.46-7.36 (m, 4H), 7.15 (d, 1H), 7.09-7.04 (m, 2H), 6.80-6.75 (m, 2H), 6.03 (t, 1H), 3.49 (s, 2H), 3.04 (q, 2H), 2.26 (t, 2H), 2.12 (s, 6H); 2.02 (s, 6H), 1.63 (p, 2H).

25 **B127: (E)-1-(2-Dimethylaminomethyl-4-methoxy-phenyl)-3-[5-(3-dimethylamino-propylamino)-2'-methyl-biphenyl-3-yl]-propenone**

General Procedure I gave the fumarate salt of title compound as yellow crystals in 59% yield. ¹H-NMR (DMSO-d₆): δ 7.68 (d, 1H), 7.35 (bs, 2H), 7.26-7.18 (m, 4H), 7.09 (d, 1H), 6.96 (dd, 1H), 6.90-6.87 (m, 2H), 6.57 (t, 1H), 6.55 (s, 4H), 3.83 (s, 3H), 3.72 (s, 2H),
30 3.14 (t, 2H), 2.86 (t, 2H), 2.54 (s, 6H), 2.24 (s, 3H), 2.21 (s, 6H), 1.85 (p, 2H).

B128: (E)-1-(2-Dimethylaminomethyl-phenyl)-3-[2'-methyl-4-(4-methyl-piperazin-1-yl)-biphenyl-2-yl]-propenone

General Procedure I gave the fumarate salt of title compound as yellow crystals in 57% yield. ¹H-NMR (DMSO-d₆): δ 7.50 (bs, 1H), 7.44-7.32 (m, 4H), 7.27 (d, 1H), 7.23-7.12 (m, 3H), 7.09-7.05 (m, 2H), 7.00-6.92 (m, 2H), 6.59 (s, 4H), 3.52 (s, 2H), 3.35 (t, 4H), 2.69 (t, 4H), 2.38 (s, 3H), 2.06 (s, 6H), 1.94 (s, 3H).

40 **B129: (E)-1-(2-Dimethylaminomethyl-4-methoxy-phenyl)-3-[2'-methyl-4-(4-methyl-piperazin-1-yl)-biphenyl-2-yl]-propenone**

General Procedure I gave the fumarate salt of title compound as yellow crystals in 36% yield. ¹H-NMR (DMSO-d₆): δ 7.57 (d, 1H), 7.51 (d, 1H), 7.37 (d, 1H), 7.26-7.18 (m, 3H), 7.12-7.06 (m, 5H), 6.91 (dd, 1H), 6.59 (s, 4H), 3.82 (s, 3H), 3.63 (s, 2H), 3.31 (t, 4H), 2.60 (t, 4H), 2.32 (s, 3H), 2.16 (s, 6H), 1.96 (s, 3H).

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B130: (E)-1-(2-Dimethylaminomethyl-phenyl)-3-[2'-methyl-5-(4-methyl-[1,4]diazepan-1-yl)-biphenyl-3-yl]-propenone

General Procedure I gave the fumarate salt of title compound as orange crystals in 69% yield. ¹H-NMR (DMSO-d₆): δ 7.50-7.37 (m, 4H), 7.32 (bs, 2H), 7.29-7.21 (m, 4H), 7.03 (bs, 1H), 6.95 (bs, 1H), 6.67 (bs, 1H), 6.57 (s, 4H), 3.69 (t, 2H), 3.60 (s, 2H), 3.49 (t, 2H), 2.97 (t, 2H), 2.87 (t, 2H), 2.53 (s, 3H), 2.25 (s, 3H), 2.11 (s, 6H), 2.05 (t, 2H).

B131: (E)-1-(2-Dimethylaminomethyl-4-methoxy-phenyl)-3-[2'-methyl-5-(4-methyl-[1,4]diazepan-1-yl)-biphenyl-3-yl]-propenone

General Procedure I gave the fumarate salt of title compound as yellow crystals in 47% yield. ¹H-NMR (DMSO-d₆): δ 7.69 (d, 1H), 7.43 (bs, 2H), 7.27-7.24 (m, 4H), 7.10 (d, 1H), 7.06 (bs, 1H), 7.00-6.95 (m, 2H), 6.67 (bs, 1H), 6.56 (s, 4H), 3.83 (s, 3H), 3.73-3.70 (m, 4H), 3.50 (t, 2H), 3.00 (t, 2H), 2.90 (t, 2H), 2.54 (s, 3H), 2.26 (s, 3H), 2.22 (s, 6H), 2.07 (t, 2H).

B132: (E)-1-(2-Dimethylaminomethyl-phenyl)-3-[2'-methyl-5-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone

General Procedure I gave the title compound as green/yellow crystals in 32% yield. ¹H-NMR (DMSO-d₆): δ 7.48-7.34 (m, 4H), 7.29-7.21 (m, 7H), 7.08 (bs, 1H), 6.87 (bs, 1H), 3.51 (s, 2H), 3.22 (t, 4H), 2.43 (t, 4H), 2.23 (s, 3H), 2.21 (s, 3H), 2.03 (s, 6H).

B133: (E)-1-(2-Dimethylaminomethyl-4-methoxy-phenyl)-3-[2'-methyl-5-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone

General Procedure I gave the fumarate salt of title compound as yellow crystals in 81% yield. ¹H-NMR (DMSO-d₆): δ 7.79 (d, 1H), 7.54 (d, 1H), 7.46 (d, 1H), 7.33-7.24 (m, 5H), 7.17-7.12 (m, 2H), 7.00 (dd, 1H), 6.91 (bs, 1H), 6.58 (s, 4H), 3.84 (s, 3H), 3.81 (s, 2H), 3.30 (bs, 4H), 2.62 (bs, 4H), 2.34 (s, 3H), 2.29 (s, 6H), 2.25 (s, 3H).

B134: (E)-1-[3-(2-Dimethylamino-ethylamino)-phenyl]-3-{4-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-2'-methoxy-biphenyl-3-yl}-propenone

General Procedure I gave the fumaric acid salt of the title compound as yellow crystals in 19% yield. ¹H NMR (DMSO-d₆) δ 7.85 (d, 1H), 7.73 (d, 1H), 7.56 (d, 1H), 7.33 (dd, 1H), 7.18-7.14 (m, 3H), 7.09-7.04 (m, 2H), 6.99-6.91 (m, 2H), 6.87-6.82 (m, 2), 6.69 (dd, 1H), 6.39 (s, 3H), 3.58 (s, 3H), 3.37 (t, 2H), 3.07 (t, 2H), 2.77 (t, 4H), 2.48 (bs, 6H), 2.34 (t, 2H), 1.89 (s, 6H).

B135: (E)-1-(2-Fluoro-4-methoxy-phenyl)-3-{4-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-2'-methoxy-biphenyl-3-yl}-propenone

General Procedure I gave the fumaric acid salt of the title compound as yellow crystals in 26% yield. ¹H NMR (DMSO-d₆) δ 7.93 (d, 1H), 7.85-7.79 (m, 2H), 7.53 (dd, 1H), 7.45 (dd, 1H), 7.36-7.32 (m, 2H), 7.18-7.10 (m, 2H), 7.06-7.00 (m, 2H), 6.95-6.91 (m, 2H), 6.61 (s, 1H), 3.87 (s, 3H), 3.78 (s, 3H), 3.56 (t, 2H), 2.95 (t, 4H), 2.64 (bs, 4H).

B136: (E)-1-[3-(2-Dimethylamino-ethylamino)-phenyl]-3-[4-(4-methyl-piperazin-1-ylmethyl)-biphenyl-3-yl]-propenone

General Procedure I gave the fumaric acid salt of the title compound as yellow crystals in 6% yield. ¹H NMR (DMSO-d₆) δ 8.09 (d, 1H), 8.06 (d, 1H), 7.70-7.65 (m, 3H), 7.55 (dd, 1H), 7.39-7.26 (m, 5H), 7.16 (d, 1H), 7.12 (bs, 1H), 6.76 (dd, 1H), 6.45 (bs, 1H), 6.45 (s,

4H), 3.50 (s, 2H), 3.13 (t, 2H), 2.56 (t, 2H), 2.38-2.36 (bs, 8H), 2.36 (s, 6H), 2.24 (s, 3H).

B137: (E)-1-(2-Fluoro-4-methoxy-phenyl)-3-{2-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-phenyl}-propenone

General Procedure I gave the title compound as yellow/brown oil in 58% yield. ¹H NMR (CDCl₃) δ 8.18 (dd, 1H), 7.91 (t, 1H), 7.67 (d, 1H), 7.45 (dd, 1H), 7.39 (dt, 1H), 7.13-7.08 (m, 3H), 6.82 (dd, 1H), 6.68 (dd, 1H), 3.90 (s, 3H), 3.70 (t, 2H), 3.07 (t, 4H), 2.79 (bs, 4H), 2.70 (t, 2H).

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B138: (E)-1-(2-Fluoro-4-methoxy-phenyl)-3-[2-(4-methyl-piperazin-1-yl)-5-pyridin-2-yl-phenyl]-propenone

General Procedure I gave the title compound as yellow/brown oil in 34% yield. ¹H NMR (CDCl₃) δ 8.70 (d, 1H), 8.31 (d, 1H), 8.16 (dd, 1H), 8.00 (dd, 1H), 7.90 (t, 1H), 7.77-7.72 (m, 2H), 7.56 (dd, 1H), 7.25-7.21 (m, 1H), 7.17 (d, 1H), 6.82 (dd, 1H), 6.69 (dd, 1H), 3.90 (s, 3H), 3.12 (t, 4H), 2.68 (bs, 4H), 2.41 (s, 3H).

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B139: (E)-3-[4-Chloro-5-(1,1-dimethyl-allyl)-2-methoxy-phenyl]-1-[4-methoxy-2-(4-methyl-piperazin-1-yl)-phenyl]-propenone

General Procedure I gave the title compound as yellow/brown oil in 31% yield. ¹H NMR (CDCl₃) δ 8.00 (d, 1H), 7.70-7.62 (m, 3H), 6.93 (s, 1H), 6.62-6.56 (m, 2H), 6.11 (dd, 1H), 5.00 (dd, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.08 (t, 4H), 2.47 (bs, 4H), 2.22 (s, 3H), 1.54 (s, 6H).

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B140: (E)-3-[2'-Methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-1-[4-methoxy-2-(4-methyl-piperazin-1-yl)-phenyl]-propenone

General Procedure I gave the title compound as yellow crystals in 29% yield. ¹H NMR (CDCl₃) δ 8.12 (d, 1H), 7.89 (d, 1H), 7.64-7.53 (m, 3H), 7.35-7.28 (m, 2H), 7.10 (d, 1H), 7.04-6.97 (m, 2H), 6.63-6.56 (m, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 3.06-3.05 (m, 8H), 2.64 (bs, 4H), 2.45 (bs, 4H), 2.38 (s, 3H), 2.08 (s, 3H).

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B141: (E)-3-[4-(4-Acetyl-piperazin-1-yl)-2'-methoxy-biphenyl-3-yl]-1-(2-fluoro-4-methoxy-phenyl)-propenone

General Procedure I gave the title compound as yellow crystals in 49% yield. ¹H NMR (CDCl₃) δ 8.20 (dd, 1H), 7.90 (t, 1H), 7.86 (d, 1H), 7.58 (dd, 1H), 7.49 (dd, 1H), 7.49 (dd, 1H), 7.39-7.34 (m, 2H), 7.21-7.01 (m, 3H), 6.82 (dd, 1H), 6.67 (dd, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.84 (bs, 1H), 3.70 (bs, 2H), 3.03 (t, 4H), 2.17 (s, 3H).

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B142: (E)-4-{3-[3-(2-Fluoro-4-methoxy-phenyl)-3-oxo-propenyl]-2'-methoxy-biphenyl-4-yl}-piperazine-1-carboxylic acid tert-butyl ester

General Procedure J gave the title compound as yellow crystals in 8% yield. ¹H NMR (CDCl₃) δ 8.19 (dd, 1H), 7.90 (t, 1H), 7.85 (d, 1H), 7.58 (dd, 1H), 7.47 (dd, 1H), 7.39-7.33 (m, 2H), 7.09 (t, 1H), 7.04 (t, 1H), 6.82 (dd, 1H), 6.67 (dd, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.65 (t, 4H), 2.99 (bs, 4H), 1.51 (s, 9H).

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B143: (E)-1-(2-Fluoro-4-methoxy-phenyl)-3-[2'-methoxy-4-(4-methyl-[1,4]diazepan-1-yl)-biphenyl-3-yl]-propenone

General Procedure J gave the fumaric acid salt of the title compound as yellow crystals in 9% yield. ¹H NMR (DMSO-d₆) δ 7.98 (dd, 1H), 7.83 (t, 1H), 7.80 (d, 1H), 7.50 (dd, 1H), 7.42-7.31 (m, 3H), 7.20 (d, 1H), 7.11 (dd, 1H), 7.06-6.91 (m, 3H), 6.57 (s, 2H), 3.87 (s, 3H), 3.78 (s, 3H), 3.34 (m, 4H), 3.24 (t, 4H), 2.43 (s, 3H), 2.08 (h, 2H).

B144: (E)-1-(2-Dimethylaminomethyl-phenyl)-3-[2'-methyl-4-(4-pyrrolidin-1-yl-piperidin-1-yl)-biphenyl-3-yl]-propenone

General Procedure I gave the title compound as yellow/brown oil in 44% yield. ¹H NMR (CDCl₃) δ 7.53-7.47 (m, 2H), 7.34-7.14 (m, 9H), 6.99-6.88 (m, 2H), 3.46 (s, 2H), 3.15-3.11 (m, 2H), 2.70-2.50 (m, 6H), 2.23 (s, 3H), 2.07 (s, 6H), 1.87-1.72 (m, 6H), 1.51-1.40 (m, 2H).

B145: (E)-1-(2-Dimethylaminomethyl-phenyl)-3-{2'-methyl-4-[methyl-(1-methyl-piperidin-4-yl)-amino]-biphenyl-3-yl}-propenone

General Procedure I gave the title compound as yellow oil in 9% yield. ¹H NMR (CDCl₃) δ 7.60 (d, 1H), 7.53 (d, 1H), 7.40-7.22 (m, 9H), 7.09 (d, 1H), 6.96 (d, 1H), 3.51 (s, 2H), 3.47-2.76 (m, 3H), 2.65 (s, 3H), 2.31 (s, 3H), 2.24 (s, 3H), 2.13 (s, 6H), 1.82-1.72 (m, 4H), 1.47-1.43 (m, 2H).

B146: (E)-1-(2-Dimethylaminomethyl-phenyl)-3-{4-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-2'-methyl-biphenyl-3-yl}-propenone

General Procedure I gave the title compound as yellow oil in 36% yield. ¹H NMR (CDCl₃) δ 7.68 (d, 1H), 7.61 (d, 1H), 7.44-7.24 (m, 8H), 7.08 (d, 2H), 7.02 (d, 1H), 3.66 (t, 2H), 3.55 (s, 2H), 2.99 (t, 4H), 2.58 (t, 2H), 2.55 (bs, 4H), 2.32 (s, 3H), 2.16 (s, 6H).

B147: (E)-1-(2-Dimethylaminomethyl-phenyl)-3-{4-[(3-dimethylamino-propyl)-methyl-amino]-2'-methyl-biphenyl-3-yl}-propenone

General Procedure I gave the title compound as orange oil in 26% yield. ¹H NMR (DMSO-d₆) δ 7.71 (d, 1H), 7.62 (d, 1H), 7.45-7.14 (m, 11H), 3.49 (s, 2H), 2.91 (t, 2H), 2.65 (s, 3H), 2.60 (s, 3H), 2.11-1.89 (m, 18H), 1.57-1.52 (m, 2H).

B148: (E)-3-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-2'-methyl-biphenyl-3-yl}-1-(2-dimethylaminomethyl-phenyl)-propenone

General Procedure I gave the title compound as orange oil in 11% yield. ¹H NMR (DMSO-d₆) δ 7.70 (d, 1H), 7.61 (d, 1H), 7.46-7.23 (m, 9H), 7.21 (d, 1H), 7.17 (d, 1H), 3.50 (s, 2H), 2.97 (t, 2H), 2.71 (s, 3H), 2.32 (t, 2H), 2.27 (s, 3H), 2.06 (s, 6H), 2.03 (s, 6H).

B149: (E)-N-(2-{3-[3',5'-Dimethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-acryloyl}-phenyl)-benzenesulfonamide

General Procedure I gave the title compound as orange crystals in 37% yield. ¹H NMR (DMSO-d₆) δ 11.20 (bs, 1H), 8.11 (dd, 1H), 7.88 (d, 1H), 7.78-7.75 (m, 3H), 7.69 (dd,

1H), 7.60-7.48 (m, 4H), 7.36(dd, 1H), 7.33 (bs, 2H), 7.25 (t, 1H), 7.20 (d, 1H), 6.98 (bs, 1H), 2.96 (t, 4H), 2.54 (bs, 4H), 2.34 (s, 6H), 2.29 (t, 3H).

B150: (E)-Propane-1-sulfonic acid (2-{3-[3',5'-dimethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-acryloyl}-phenyl)-amide

General Procedure I gave the title compound as orange crystals in 38% yield. ¹H NMR (DMSO-d₆) δ 11.03 (s, 1H), 8.31 (d, 1H), 8.15 (d, 1H), 8.08 (d, 1H), 7.96 (d, 1H), 7.69-7.61 (m, 3H), 7.33-7.28 (m 3H), 7.19 (d, 1H), 6.98 (s, 1H), 3.32 (bs, 1H), 3.26 (t, 2H), 2.95 (bs, 4H), 2.34 (bs, 6H), 2.26 (s, 3H), 1.75-1.62 (m, 2H), 0.93 (t, 3H).

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B151: (E)-N-(2-{3-[3',5'-Dimethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-acryloyl}-phenyl)-methanesulfonamide

General Procedure I gave the title compound as orange crystals in 22% yield. ¹H NMR (DMSO-d₆) δ 10.96 (s, 1H), 8.29 (d, 1H), 8.15 (d, 1H), 8.06 (d, 1H), 7.94 (d, 1H), 7.70-7.65 (m, 2H), 7.61 (d, 1H) 7.30 (d, 1H), 7.20 (d, 1H), 6.99 (s, 1H), 3.18 (s, 3H), 2.95 (t, 4H), 2.50 (t, 4H), 2.35 (s, 6H), 2.27 (s, 3H).

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B152: (E)-3-(5-tert-Butyl-2-methoxy-phenyl)-1-[2-fluoro-6-(4-methyl-piperazin-1-yl)-phenyl]-propenone

General Procedure I gave the title compound as orange crystals in 62% yield. ¹H NMR (CDCl₃) δ 7.65 (d, 1H), 7.48 (d, 1H), 7.30-7.22 (m, 2H), 7.05 (d, 1H), 6.80-6.77 (m, 3H), 3.75 (s, 3H), 3.14 (bs, H), 2.55 (bs, 4H), 2.34 (s, 3H), 1.24 (s, 9H).

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B153: (E)-3-[3',5'-Dimethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-1-[2-fluoro-6-(4-methyl-piperazin-1-yl)-phenyl]-propenone

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General Procedure I gave the title compound as orange crystals in 9% yield. ¹H NMR (DMSO-d₆) δ 8.01 (d, 1H), 7.69-7.63 (m, 2H), 7.47 (q, 1H), 7.33 (bs, 2H), 7.15 (d, 1H), 7.05-6.95 (m, 3H), 2.94 (t 4H), 2.84 (t, 4H), 2.33-2.30 (m, 12H), 2.19 (s, 3H), 2.06 (s, 3H).

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B154: (E)-1-[2,6-Bis-(4-methyl-piperazin-1-yl)-phenyl]-3-(3-dibutylamino-phenyl)-propenone

General Procedure I gave the title compound as yellow oil in 13% yield. ¹H NMR (CDCl₃) δ 7.33 (t, 1H), 7.21-7.15 (m, 2H), 6.91-6.81 (m, 2H), 7.80-6.74 (m, 2H), 6.65 (dd, 1H), 3.27 (t, 4H), 3.02 (bs, 8H), 2.45 (bs, 8H), 2.27 (bs, 6H), 1.61-1.51 (m, 4H), 1.42-1.28 (m, 4H), 0.95 (t, 6H).

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B155: (E)-1-[2,4-Bis-(4-methyl-piperazin-1-yl)-phenyl]-3-(3-dibutylamino-phenyl)-propenone

General Procedure I gave the title compound as yellow oil in 24% yield. ¹H NMR (CDCl₃) δ 7.64 (t, 3H), 7.20 (d, 1H), 6.95 (d, 1H), 6.82 (bs, 1H), 6.66 (dd, 1H), 6.59 (dd, 1H), 6.47 (d, 1H), 3.35 (t, 4H), 3.28 (t, 4H), 3.13 (bs, 4H), 2.58 (t, 8H), 2.37 (s, 3H), 2.27 (s, 3H), 1.63-1.53 (m, 4H), 1.42-1.30 (m, 4H), 0.96 (t, 6H).

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B156 : (E)-3-(3-Dibutylamino-phenyl)-1-[2-fluoro-6-(4-methyl-piperazin-1-yl)-phenyl]-propenone

General Procedure I gave the title compound as yellow oil in 25% yield. ¹H NMR (CDCl₃) δ7.46 (d, 1H), 7.36-7.32 (m, 1H), 7.20 (t, 1H), 7.02 (d, 1H), 6.89-6.77 (m, 4H), 6.68 (dd, 1H), 3.28 (t, 4H), 3.07 (t, 4H), 2.45 (t, 4H), 2.25 (s, 3H), 1.59-1.52 (m, 4H), 1.40-1.30 (m, 4H), 0.96 (t, 6H).

B157: (E)-1-[2,4-Bis-(4-methyl-piperazin-1-yl)-phenyl]-3-[5-bromo-2-(4-methyl-piperazin-1-yl)-phenyl]-propenone

10 General Procedure I gave the title compound as yellow foam in 38% yield. ¹H NMR (CDCl₃) δ7.96 (d, 1H), 7.88 (d, 1H), 7.68-7.63 (m, 2H), 7.42 (dd, 1H), 6.96 (d, 1H), 6.61 (dd, 1H), 6.50 (d, 1H), 3.46 (t, 4H), 3.14 (bs, 4H), 3.05 (bs, 4H), 2.75 (bs, 4H), 2.60 (bs, 4H), 2.57 (t, 4H), 2.45 (s, 3H), 2.37 (s, 6H).

15 B158: (E)-1-[2,4-Bis-(4-methyl-piperazin-1-yl)-phenyl]-3-[3',5'-dimethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone

General Procedure I gave the title compound as yellow powder in 30% yield. ¹H NMR (CDCl₃) δ8.13 (d, 1H), 7.94 (d, 1H), 7.74 (d, 1H), 7.65 (d, 1H), 7.55 (dd, 1H), 7.21 (bs, 2H), 7.12 (d, 1H), 6.97 (bs, 1H), 6.59 (dd, 1H), 6.48 (d, 1H), 3.34 (t, 4H), 3.09-3.08 (m, 8H), 2.71 (bs, 4H), 2.58-2.55 (m, 8H), 2.42 (s, 3H), 2.37 (s, 6H), 2.36 (s, 3H), 2.12 (s, 3H).

B159: (E)-1-[2,4-Bis-(4-methyl-piperazin-1-yl)-phenyl]-3-(5-tert-butyl-2-methoxy-phenyl)-propenone

25 General Procedure I gave the fumaric acid salt of the title compound as yellow crystals in 25% yield. ¹H NMR (DMSO-d₆) δ7.94 (d, 1H), 7.80 (d, 1H), 7.73 (d, 1H), 7.47-7.42 (m, 2H), 7.03 (d, 1H), 6.64 (s, 2H), 6.49 (d, 1H), 3.86 (s, 3H), 3.32 (bs, 4H), 2.99 (bs, 4H), 2.55 (bs, 4H), 2.49 (bs, 4H), 2.29 (s, 3H), 2.11 (s, 3H), 1.31 (s, 9H).

30 B160 : (E)-1-[2,4-Bis-(4-methyl-piperazin-1-yl)-phenyl]-3-(2,4-dichloro-phenyl)-propenone

General Procedure I gave the title compound as yellow crystals in 62% yield. ¹H NMR (CDCl₃) δ7.53-7.32 (m, 6H), 7.08 (d, 1H), 6.90 (d, 1H), 6.83 (t, 1H), 3.51 (s, 2H), 3.12 (bs, 4H), 2.52 (bs, 4H), 2.30 (bs, 9H).

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B161 : (E)-1-[2,4-Bis-(4-methyl-piperazin-1-yl)-phenyl]-3-(3-dimethylaminomethyl-phenyl)-propenone

General Procedure I gave the title compound as yellow foam in 50% yield. ¹H NMR (CDCl₃) δ8.11 (d, 1H), 7.90 (d, 1H), 7.68 (d, 1H), 7.64 (d, 1H), 7.54 (dd, 1H), 7.35-7.28 (m, 2H), 7.11 (d, 1H), 7.04-6.97 (m, 2H), 6.59 (dd, 1H), 6.47 (d, 1H), 3.80 (s, 3H), 3.33 (t, 4H), 3.09-3.07 (m, 8H), 2.69 (bs, 4H), 2.56 (t, 4H), 2.46 (bs, 4H), 2.41 (s, 3H), 2.36 (s, 3H), 2.06 (s, 3H).

B162 : (E)-3-[3',5'-Dimethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-1-[2-(4-methyl-piperazin-1-yl)-phenyl]-propenone

General Procedure I gave the title compound as yellow foam in 31% yield. ¹H NMR (CDCl₃) δ8.09 (d, 1H), 7.92 (d, 1H), 7.60-7.43 (m, 4H), 7.21 (bs, 2H), 7.15-7.09 (m, 3H), 6.99 (bs, 1H), 3.12-3.10 (m, 8H), 2.71 (bs, 4H), 2.56 (bs, 4H), 2.45 (s, 3H), 2.38 (s, 6H), 2.19 (s, 3H).

B163: (E)-3-(2,4-Dichloro-phenyl)-1-[2-fluoro-6-(4-methyl-piperazin-1-yl)-phenyl]-propenone

10 General Procedure I gave the title compound as yellow powder in 38% yield. ¹H NMR (CDCl₃) δ7.81 (d, 1H), 7.62 (d, 1H), 7.45 (d, 1H), 7.40-7.27 (m, 2H), 6.99 (d, 1H), 6.91-6.80 (m, 2H), 3.05 (t, 4H), 2.41 (t, 4H), 2.23 (s, 3H).

B164: (E)-1-[2,4-Bis-(4-methyl-piperazin-1-yl)-phenyl]-3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone

15 General Procedure I gave the title compound as yellow crystals in 52% yield. ¹H NMR (CDCl₃) δ8.11 (d, 1H), 7.90 (d, 1H), 7.68 (d, 1H), 7.64 (d, 1H), 7.54 (dd, 1H), 7.35-7.28 (m, 2H), 7.11 (d, 1H), 7.04-6.97 (m, 2H), 6.59 (dd, 1H), 6.47 (d, 1H), 3.80 (s, 3H), 3.33 (t, 4H), 3.09-3.07 (m, 8H), 2.69 (bs, 4H), 2.56 (t, 4H), 2.46 (bs, 4H), 2.41 (s, 3H), 2.36 (s, 3H), 2.06 (s, 3H).

B165 : (E)-3-(3-Dimethylaminomethyl-phenyl)-1-[2-fluoro-6-(4-methyl-piperazin-1-yl)-phenyl]-propenone

25 General Procedure I gave the title compound as yellow oil in 52% yield. ¹H NMR (CDCl₃) δ7.53-7.32 (m, 6H), 7.08 (d, 1H), 6.90 (d, 1H), 6.83 (t, 1H), 3.51 (s, 2H), 3.12 (bs, 4H), 2.52 (bs, 4H), 2.30 (bs, 9H).

B166: (E)-1-[2-Fluoro-6-(4-methyl-piperazin-1-yl)-phenyl]-3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone

30 General Procedure I gave the title compound as yellow powder in 68% yield. ¹H NMR (CDCl₃) δ7.81-7.75 (m, 2H), 7.54 (dd, 1H), 7.38-7.30 (m, 3H), 7.09-6.98 (m, 4H), 6.92-6.80 (m, 2H), 3.83 (s, 3H), 3.04 (t, 4H), 2.98 (t, 4H), 2.41 (bs, 8H), 2.32 (s, 3H), 2.23 (s, 3H).

B167: (E)-3-[5-Bromo-2-(4-methyl-piperazin-1-yl)-phenyl]-1-[2-(4-methyl-piperazin-1-yl)-phenyl]-propenone

35 General Procedure I gave the title compound as yellow powder in 24% yield. ¹H NMR (CDCl₃) δ7.96 (d, 1H), 7.86 (d, 1H), 7.57 (dd, 1H), 7.48-7.40 (m, 3H), 7.12-7.07 (m, 2H), 6.94 (d, 1H), 3.08 (t, 4H), 2.97 (t, 4H), 2.60 (bs, 4H), 2.52 (bs, 4H), 2.37 (s, 3H), 2.29 (s, 3H).

B168: (E)-3-(5-tert-Butyl-2-methoxy-phenyl)-1-[2-(4-methyl-piperazin-1-yl)-phenyl]-propenone

General Procedure I gave the title compound as yellow crystals in 29% yield. ^1H NMR (CDCl_3) δ 8.10 (d, 1H), 7.67 (d, 1H), 7.60 (d, 1H), 7.57 (dd, 1H), 7.44-7.37 (m, 2H), 6.87 (d, 1H), 3.87 (s, 3H), 3.10 (t, 4H), 2.50 (t, 4H), 2.23 (s, 3H), 1.33 (s, 9H).

5 **B169: (E)-3-(3-Dibutylamino-phenyl)-1-[2-(4-methyl-piperazin-1-yl)-phenyl]-propenone**

General Procedure I gave the title compound as yellow oil in 81% yield. ^1H NMR (CDCl_3) δ 7.66 (d, 1H), 7.57 (dd, 1H), 7.48-7.42 (m, 2H), 7.21 (d, 1H), 7.12-7.07 (m, 2H), 6.93 (d, 1H), 6.82 (bs, 1H), 6.68 (dd, 1H), 3.29 (t, 4H), 3.11 (t, 4H), 2.53 (bs, 4H), 2.26 (s, 3H),
10 1.63-1.53 (m, 4H), 1.42-1.30 (m, 4H), 0.96 (t, 6H).

B170: (E)-3-(2,4-Dichloro-phenyl)-1-[2-(4-methyl-piperazin-1-yl)-phenyl]-propenone

General Procedure I gave the title compound as yellow oil in 30% yield. ^1H NMR (CDCl_3) δ
15 8.01 (d, 1H), 7.67 (d, 1H), 7.58 (dd, 1H), 7.49-7.43 (m, 3H), 7.28 (ddd, 1H), 7.13-7.08 (m, 2H), 3.08 (t, 4H), 2.45 (bs, 4H), 2.22 (s, 3H).

B171: (E)-3-(3-Dimethylaminomethyl-phenyl)-1-[2-(4-methyl-piperazin-1-yl)-phenyl]-propenone

20 General Procedure I gave the title compound as yellow oil in 61% yield. ^1H NMR (CDCl_3) δ 7.69 (d, 1H), 7.59-7.56 (m, 2H), 7.53-7.36 (m, 5H), 7.12-7.07 (m, 2H), 3.48 (s, 2H), 3.10 (t, 4H), 2.50 (bs, 4H), 2.27 (s, 6H), 2.22 (s, 3H).

25 **B172: (E)-3-[2'-Methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-1-[2-(4-methyl-piperazin-1-yl)-phenyl]-propenone**

General Procedure I gave the title compound as yellow crystals in 24% yield. ^1H NMR (CDCl_3) δ 8.07 (d, 1H), 7.87 (d, 1H), 7.58-7.53 (m, 2H), 7.47-7.41 (m, 2H), 7.34-7.30 (m, 2H), 7.26-6.97 (m, 5H), 3.81 (s, 3H), 3.07-3.06 (m, 8H), 2.64 (bs, 4H), 2.47 (bs, 4H), 2.41 (s, 3H), 2.13 (s, 3H).

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B173: (E)-3-(5-tert-Butyl-2-methoxy-phenyl)-1-[4-hydroxy-2-(4-methyl-piperazin-1-yl)-phenyl]-propenone

General Procedure I gave the title compound as yellow foam in 16% yield. ^1H NMR (CDCl_3) δ 8.03 (d, 1H), 7.64-7.56 (m, 3H), 7.39 (dd, 1H), 6.88 (d, 1H), 6.63-6.58 (m, 2H), 3.87 (t, 4H), 3.18 (t, 4H), 2.72 (bs, 4H), 2.36 (s, 3H), 1.33 (s, 9H).
35

B174: (E)-3-(3,5-Di-tert-butyl-2-methoxy-phenyl)-1-[4-hydroxy-2-(4-methyl-piperazin-1-yl)-phenyl]-propenone

General Procedure I gave the title compound as yellow crystals in 91% yield. ^1H NMR ($\text{CDCl}_3 + \text{MeOH}$) δ 7.81 (d, 1H), 7.71 (d, 1H), 7.46-7.44 (m, 2H), 6.21 (dd, 1H), 6.16 (d, 1H), 3.65 (s, 3H), 2.89 (bs, 4H), 2.37 (bs, 4H), 2.05 (s, 3H), 1.28 (s, 9H), 1.21 (s, 9H).
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B175: (E)-1-(3-Fluoro-4-hydroxy-phenyl)-3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone

General Procedure I gave the title compound as yellow powder in 75% yield. ¹H NMR (DMSO-d₆) δ 7.86 (d, 1H), 7.73-7.63 (m, 2H), 7.56 (dd, 1H), 7.37-7.27 (m, 4H), 7.19 (d, 1H), 7.13-7.10 (m, 2H), 7.03 (dt, 1H), 3.77 (s, 3H), 2.85 (t, 4H), 2.26 (bs, 4H), 2.17 (s, 3H).

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B176: (E)-1-(3-Dimethylaminomethyl-4-hydroxy-phenyl)-3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone

General Procedure I gave the title compound as yellow crystals in 10% yield. ¹H NMR (CDCl₃) δ 8.20 (d, 1H), 7.93 (dd, 1H), 7.78 (dd, 2H), 7.55 (d, 1H), 7.54 (d, 1H), 7.37-7.31 (m, 2H), 7.12 (d, 1H), 7.08-6.98 (m, 3H), 6.88 (d, 1H), 3.84 (s, 3H), 3.74 (s, 2H), 3.08 (t, 4H), 2.67 (bs, 4H), 2.39 (s, 3H), 2.36 (s, 6H).

B177: (E)-2-Dimethylamino-N-(3-{3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-acryloyl}-phenyl)-acetamide

General Procedure I gave the title compound as orange crystals in 16% yield. ¹H NMR (DMSO-d₆) δ 10.12 (bs, 1H), 8.34 (bs, 1H), 8.06 (d, 1H), 7.97-7.94 (m, 2H), 7.87 (d, 1H), 7.79 (d, 1H), 7.56-7.47 (m, 2H), 7.38-7.32 (m, 2H), 7.19 (d, 1H), 7.12 (d, 1H), 7.04 (t, 1H), 6.60 (s, 4H), 3.78 (s, 3H), 3.29 (s, 2H), 3.04 (t, 4H), 2.81 (bs, 4H), 2.46 (s, 3H), 2.39 (s, 6H).

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B178: (E)-1-(2,6-Difluoro-phenyl)-3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone

General Procedure I gave the title compound as yellow crystals in 40% yield. ¹H NMR (CDCl₃) δ 7.87 (d, 1H), 7.73-7.63 (m, 2H), 7.56 (dd, 1H), 7.37-7.27 (m, 4H), 7.21-7.10 (m, 3H), 7.02 (dt, 1H), 3.77 (s, 3H), 2.85 (t, 4H), 2.26 (bs, 4H), 2.17 (s, 3H).

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B179: (E)-1-(3-Fluoro-4-methoxy-phenyl)-3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone

General Procedure I gave the title compound as yellow crystals in 66% yield. ¹H NMR (DMSO-d₆) δ 8.12-7.99 (m, 4H), 7.88 (d, 1H), 7.52 (dd, 1H), 7.38-7.28 (m, 3H), 7.18-7.11 (m, 2H), 7.04 (dt, 1H), 3.95 (s, 3H), 3.78 (s, 3H), 2.95 (t, 4H), 2.54 (bs, 4H), 2.27 (s, 3H).

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B180: (E)-1-(2-Fluoro-4-methoxy-phenyl)-3-[4'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone

General Procedure J gave the fumaric acid salt of the title compound as yellow crystals in 54% yield. ¹H NMR (DMSO-d₆) δ 7.98 (d, 1H), 7.95 (d, 1H), 7.82 (t, 1H), 7.67-7.63 (m, 3H), 7.58 (dd, 1H), 7.19 (d, 1H), 7.04-6.93 (m, 4H), 6.60 (s, 2H), 3.88 (s, 3H), 3.80 (s, 3H), 2.94 (t, 4H), 2.54 (bs, 4H), 2.29 (s, 3H).

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B181: (E)-1-(2-Fluoro-4-methoxy-phenyl)-3-[3'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone

General Procedure J gave the fumaric acid salt of the title compound as yellow crystals in 30% yield. ¹H NMR (DMSO-d₆) δ 8.03 (d, 1H), 7.90 (d, 1H), 7.83 (t, 1H), 7.71 (dd, 1H),

7.61 (dd, 1H), 7.38 (t, 1H), 7.29-7.20 (m, 3H), 7.02-6.91 (m, 3H), 6.61 (s, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 2.96 (t, 4H), 2.51 (bs, 4H), 2.07 (s, 3H).

B182: (E)-3-[3',5'-Dimethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-1-(2-fluoro-4-methoxy-phenyl)-propenone

General Procedure J gave the fumaric acid salt of the title compound as yellow crystals in 44% yield. ¹H NMR (DMSO-d₆) δ 8.00 (d, 1H), 7.90 (d, 1H), 7.83 (t, 1H), 7.68 (dd, 1H), 7.59 (dd, 1H), 7.31 (bs, 2H), 7.20 (d, 1H), 7.02-6.93 (m, 3H), 6.61 (s, 3H), 3.88 (s, 3H), 2.98 (t, 4H), 2.63 (bs, 4H), 2.35 (s, 3H), 2.34 (s, 6H).

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B183: (E)-1-(2-Fluoro-4-methoxy-phenyl)-3-[2-(4-methyl-piperazin-1-yl)-5-pyridin-3-yl-phenyl]-propenone

General Procedure J gave the title compound as yellow crystals in 57% yield. ¹H NMR (DMSO-d₆) δ 8.96 (d, 1H), 8.55 (dd, 1H), 8.15-8.11 (m, 2H), 7.89 (d, 1H), 7.82 (d, 1H), 7.77 (dd, 1H), 7.64 (dd, 1H), 7.47 (dd, 1H), 7.23 (d, 1H), 7.01-6.92 (m, 2H), 3.87 (s, 3H), 2.95 (t, 4H), 2.48 (bs, 4H), 2.24 (s, 3H).

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B184: (E)-1-(4-Hydroxy-phenyl)-3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone

General Procedure I gave the fumaric acid salt of the title compound as yellow crystals in 70% yield. ¹H NMR (DMSO-d₆) δ 8.06 (d, 2H), 8.03 (d, 1H), 7.95 (d, 1H), 7.84 (d, 1H), 7.51 (dd, 1H), 7.38-7.32 (m, 3H), 7.16 (d, 1H), 7.11 (d, 1H), 7.03 (dt, 1H), 6.89 (d, 2H), 6.57 (s, 2H), 3.77 (s, 3H), 2.98 (t, 4H), 2.64 (bs, 4H), 2.34 (s, 3H).

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B185: (E)-N-(2-{3-[2'-Methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-acryloyl}-phenyl)-benzenesulfonamide

General Procedure I gave the title compound as yellow crystals in 39% yield. ¹H NMR (DMSO-d₆) δ 8.08 (dd, 1H), 7.99 (d, 1H), 7.91 (d, 1H), 7.78-7.74 (m, 2H), 7.6 (d, 1H), 7.60-7.47 (m, 5H), 7.37-7.32 (m, 3H), 7.24-7.10 (m, 3H), 7.03 (dt, 1H), 3.70 (s, 3H), 2.96 (t, 4H), 2.55 (bs, 4H), 2.29 (s, 3H).

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B186: (E)-1-(2-Fluoro-4-hydroxy-phenyl)-3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone

General Procedure I gave the fumaric acid salt of the title compound as yellow crystals in 75% yield. ¹H NMR (DMSO-d₆) δ 7.93 (dd, 1H), 7.81 (d, 1H), 7.75 (t, 1H), 7.52 (dd, 1H), 7.46 (dd, 1H), 7.37-7.31 (m, 2H), 7.16 (d, 1H), 7.11 (dd, 1H), 7.03 (dt, 1H), 6.75 (dd, 1H), 6.67 (dd, 1H), 6.57 (s, 2H), 2.96 (t, 4H), 2.58 (bs, 4H), 2.31 (s, 3H).

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B187: (E)-N-[3'-[3-(2-Fluoro-4-methoxy-phenyl)-3-oxo-propenyl]-4'-(4-methyl-piperazin-1-yl)-biphenyl-4-yl]-acetamide

General Procedure J gave the title compound as yellow crystals in 52% yield. ¹H NMR (CDCl₃) δ 8.15 (dd, 1H), 7.88 (t, 1H), 7.81 (d, 1H), 7.60-7.52 (m, 5H), 7.48 (dd, 1H), 7.36 (bs, 1H), 7.12 (d, 1H), 6.80 (dd, 1H), 6.66 (dd, 1H), 3.88 (s, 3H), 3.07 (t, 3H), 2.66 (bs, 4H), 2.39 (s, 3H), 2.21 (s, 3H).

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B188: (E)-3'-[3-(2-Fluoro-4-methoxy-phenyl)-3-oxo-propenyl]-4'-(4-methyl-piperazin-1-yl)-biphenyl-4-carboxylic acid

General Procedure J gave the title compound as yellow crystals in 52% yield. ¹H NMR

- 5 (DMSO) δ 8.10 (d, 1H), 8.00 (d, 2H), 7.90-7.79 (m, 4H), 7.76 (dd, 1H), 7.60 (dd, 1H), 7.20 (d, 1H), 7.00-6.91 (m, 2H), 3.86 (s, 3H), 3.77 (bs 4H), 2.94 (t, 4H), 2.24 (s, 3H).

B189: (E)-3-[4'-Amino-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-1-(2-fluoro-4-methoxy-phenyl)-propenone

- 10 General Procedure J gave the fumaric acid salt of the title compound as yellow crystals in 28% yield. ¹H NMR (DMSO) δ 7.94-7.79 (m, 3H), 7.58 (dd, 1H), 7.54 (dd, 1H), 7.41 (d, 2H), 7.14 (d, 1H), 6.99 (dd 1H), 6.94 (dd, 1H), 6.64 (d, 2H), 6.60 (s, 2H), 3.87 (s, 3H), 2.93 (t, 4H), 2.58 (bs, 4H), 2.32 (s, 3H).

15 **B190: (E)-1-(2-Fluoro-4-methoxy-phenyl)-3-[4'-methanesulfonyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone**

General Procedure J gave the title compound as yellow crystals in 14% yield. ¹H NMR

- (CDCl₃) δ 8.17 (d, 1H), 8.05 (d, 2H), 7.95 (t, 1H), 7.90 (d, 1H), 7.81 (d, 2H), 7.65 (dd, 1H), 7.55 (dd, 1H), 7.21 (d, 1H), 6.86 (dd, 1H), 6.71 (dd, 1H), 3.93 (s, 3H), 3.14 (bs, 7H),
20 2.73 (bs, 4H), 2.45 (s, 3H).

B191: (E)-1-(2-Fluoro-4-methoxy-phenyl)-3-[3'-hydroxymethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone

General Procedure J gave the title compound as yellow crystals in 18% yield. ¹H NMR

- 25 (CDCl₃) δ 8.15 (dd, 1H), 7.88 (t, 1H), 7.84 (d, 1H), 7.59-7.33 (m, 6H), 7.10 (d, 1H), 6.80 (dd, 1H), 6.66 (dd, 1H), 4.77 (s, 2H), 3.87 (s, 3H), 3.05 (t, 4H), 2.65 (bs, 4H), 2.39 (s, 3H).

B192: (E)-1-(2-Fluoro-4-methoxy-phenyl)-3-[2-(4-methyl-piperazin-1-yl)-5-thiophen-3-yl-phenyl]-propenone

General Procedure J gave the title compound as brown crystals in 45% yield. ¹H NMR

- 30 (CDCl₃) δ 8.15 (dd, 1H), 7.89 (t, 1H), 7.84 (d, 1H), 7.58 (dd, 1H), 7.47 (dd, 1H), 7.42-7.37 (m, 3H), 7.09 (d, 1H), 6.80 (dd, 1H), 6.67 (dd, 1H), 3.87 (s, 3H), 3.04 (t, 4H), 2.63 (bs, 4H), 2.38 (s, 3H).

35 **B193: (E)-1-(2-Fluoro-4-methoxy-phenyl)-3-[4'-hydroxymethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone**

General Procedure J gave the title compound as yellow crystals in 65% yield. ¹H NMR

- (CDCl₃) δ 8.14 (dd, 1H), 7.88 (t, 1H), 7.83 (d, 1H), 7.59-7.43 (m, 6H), 7.08 (d, 1H), 6.80
40 (dd 1H), 6.66 (dd, 1H), 4.74 (s, 2H), 3.87 (s, 3H), 3.03 (t, 4H), 2.64 (bs, 4H), 2.37 (s, 3H).

B194: (E)-1-(2-Fluoro-4-methoxy-phenyl)-3-[4-(4-methyl-piperazin-1-yl)-4'-trifluoromethyl-biphenyl-3-yl]-propenone

General Procedure J gave the title compound as yellow crystals in 24% yield. ¹H NMR (CDCl₃) δ 8.15 (dd, 1H), 7.90 (t, 1H), 7.84 (d, 1H), 7.69 (s, 4H), 7.60 (dd, 1H), 7.50 (dd, 1), 7.16 (d, 1H), 6.81 (dd, 1H), 6.67 (dd, 1H), 3.89 (s, 3H), 3.10 (t, 4H), 2.68 (bs, 4H), 2.41 (s, 3H).

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B195: (E)-1-(2-Fluoro-4-methoxy-phenyl)-3-[2'-fluoro-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone

General Procedure J gave the title compound as yellow crystals in 45% yield. ¹H NMR (CDCl₃) δ 8.16 (dd, 1H), 7.88 (t, 1H), 7.81 (t, 1H), 7.55 (dt, 1H), 7.49-7.41 (m, 2H), 7.35-
10 7.28 (m, 1H), 7.23 (dd, 1H), 7.18 (dd, 1H), 7.14 (dd, 1H), 6.80 (dd, 1H), 6.65 (dd, 1H), 3.87 (s, 3H), 3.08 (t, 4H), 2.65 (bs, 4H), 2.39 (s, 3H).

B196: (E)-1-(2-Fluoro-4-methoxy-phenyl)-3-[4-(4-methyl-piperazin-1-yl)-3'-trifluoromethyl-biphenyl-3-yl]-propenone

15 General Procedure J gave the title compound as yellow crystals in 19% yield. ¹H NMR (CDCl₃) δ 8.15 (dd, 1H), 7.89 (t, 1H), 7.83-7.74 (m, 3H), 7.61-7.55 (m, 3H), 7.50 (dd, 1H), 7.16 (d, 1H), 6.80 (dd, 1H), 6.67 (dd, 1H), 3.88 (s, 3H), 3.09 (t, 4H), 2.66 (bs, 4H), 2.40 (s, 3H).

20 **B197: (E)-1-(2-Fluoro-4-methoxy-phenyl)-3-[4'-fluoro-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone**

General Procedure J gave the title compound as yellow crystals in 53% yield. ¹H NMR (CDCl₃) δ 8.15 (dd, 1H), 7.89 (t, 1H), 7.79 (d, 1H), 7.55-7.45 (m, 4H), 7.16-7.10 (m, 3H), .81 (dd, 1H), 6.67 (dd, 1H), 3.88 (s, 3H), 3.07 (t, 4H), 2.65 (bs, 4H), 2.39 (s, 3H).

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B198: (E)-1-(2-Fluoro-4-methoxy-phenyl)-3-[3'-fluoro-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone

General Procedure J gave the title compound as yellow crystals in 33% yield. ¹H NMR (CDCl₃) 8.15 (dd, 1H), 7.90 (t, 1H), 7.82 (d, 1H), 7.57 (dd, 1H), 7.49 (dd, 1H), 7.44-
30 7.27(m, 3H), 7.14 (d, 1H), 7.06-7.00 (m, 1H), 6.81 (dd, 1H), 6.67 (dd, 1H), 3.88 (s, 3H), 3.09 (t, 4H), 2.67 (bs, 4H), 2.40 (s, 3H).

B199 : (E)-3-[5-Bromo-2-(4-methyl-piperazin-1-yl)-phenyl]-1-(2-fluoro-4-methoxy-phenyl)-propenone

35 General Procedure I gave the title compound as yellow crystals in 79% yield. ¹H NMR (CDCl₃) 8.02 (dd, 1H), 7.88 (t, 1H), 7.73 (d, 1H), 7.43 (dd, 1H), 7.38 (dd, 1H), 6.93 (d, 1H), 6.79 (dd, 1H), 6.66 (dd, 1H), 3.88 (s, 3H), 2.98 (t, 4H), 2.61 (bs, 4H), 2.36 (s, 3H).

40 **B200 : 2-Dimethylamino-N-[3-(3-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl})-(E)-acryloyl]-phenyl]-acetamide**

General Procedure I gave the title product as orange oil in 5% yield. ¹H-NMR (CDCl₃) δ 9.24 (br, 1H), 8.02 (d, 1H), 7.99-7.95 (m, 1H), 7.71 (d, 1H), 7.69-7.66 (m, 1H), 7.45-

7.38 (m, 2H), 7.22-7.17 (m 1H), 6.97 (d, 1H), 6.85 (s, 1G), 6.70 (dd, 1H), 3.46 (t, 2H), 3.04 (s, 2H), 2.94 (s, 3H), 2.47 (t, 2H), 2.33 (s, 6H), 2.28 (s, 6H).

B201: (E)-3-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(3-dimethylaminomethyl-4-hydroxy-phenyl)-propenone

General Procedure I gave the title product as orange semi-solid in 23% yield. ¹H-NMR (DMSO-d₆) δ 8.00 (dd, 1H), 7.92 (d, 1H), 7.80 (d, 1H), 7.62 (d, 1H), 7.24 (t, 1H), 7.12 (d, 1H), 7.06 (br s, 1H), 6.85 (d, 1H), 6.77 (dd, 1H), 3.70 (s, 2H), 3.45 (t, 2H), 2.96 (s, 3H), 2.38 (t, 2H), 2.28 (s, 6H), 2.20 (s, 6H).

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B202: (E)-3-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(4-hydroxy-phenyl)-propenone

General Procedure I gave the title product as yellow crystals in 17% yield. ¹H-NMR (DMSO-d₆) δ 8.05 (dt, 2H), 7.80 (d, 1H), 7.62 (d, 1H), 7.12-7.05 (m, 2H), 6.90 (dt, 2H), 6.77 (dd, 1H), 3.47 (t, 2H), 2.96 (s, 3H), 2.39 (t, 2H), 2.19 (s, 6H).

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B203: (E)-3-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(3-hydroxy-phenyl)-propenone

General Procedure I gave the title product as yellow crystals in 50% yield. ¹H-NMR (DMSO-d₆) δ 9.80 (br, 1H), 7.75 (d, 1H), 7.65 (d, 1H), 7.60 (dt, 1H), 7.44 (t, 1H), 7.37 (t, 1H), 7.24 (t, 1H), 7.13-7.03 (m, 3H), 6.78 (dd, 1H), 3.47 (t, 2H), 2.95 (s, 3H), 2.38 (t, 2H), 2.18 (s, 6H).

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B204: (E)-3-[4-Bromo-2-(4-methyl-piperazin-1-yl)-phenyl]-1-(3-dimethylaminomethyl-4-hydroxy-phenyl)-propenone

General Procedure I gave the fumaric acid salt of the title product as yellow crystals in 27% yield. ¹H-NMR (DMSO-d₆) δ 8.05-7.99 (m, 2H), 7.87-7.83 (m, 3H), 7.32-7.25 (m, 2H), 6.92 (d, 1H), 6.59 (s, 4H), 3.87 (s, 3H), 2.94 (t, 4H), 2.59 (br, 4H), 2.42 (s, 6H), 2.31 (s, 3H).

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B205: N-(3-{3-[4-Bromo-2-(4-methyl-piperazin-1-yl)-phenyl]}-(E)-acryloyl)-2-dimethylamino-acetamide

General Procedure I gave the fumaric acid salt of the title product as yellow crystals in 15% yield. ¹H-NMR (DMSO-d₆) δ 9.99 (br, 1H), 8.33 (t, 1H), 7.98 (dd, 1H), 7.89 (d, 1H), 7.87-7.81 (m, 2H), 7.77 (d, 1H), 7.51 (t, 1H), 7.34-7.27 (m, 2H), 6.61 (s, 4H), 3.17 (s, 3H), 2.95 (t, 4H), 2.57 (br, 4H), 2.34 (s, 6H), 2.29 (s, 3H).

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B206: (E)-1-(2-Dimethylaminomethyl-phenyl)-3-[2'-methyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone

General Procedure I gave the fumaric acid salt of the title product as yellow crystals in 22% yield. ¹H-NMR (DMSO-d₆): δ 7.77 (d, 1H), 7.63 (d, 1H), 7.59-7.38 (m, 4H), 7.35 (dd, 1H), 7.28-7.21 (m, 5H), 7.16 (d, 1H), 6.60 (s, 4H), 3.60 (s, 2H), 2.90 (t, 4H), 2.39 (br, 4H), 2.25 (s, 3H), 2.24 (s, 3H), 2.14 (s, 6H).

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B207: (E)-1-(3-Dimethylaminomethyl-phenyl)-3-[2'-methyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone

General Procedure I gave the fumaric acid salt of the title product as yellow crystals in 23% yield. ¹H-NMR (DMSO-d₆): δ 8.09 (d, 1H), 8.08 (d, 2H), 7.93 (d, 1H), 7.89 (d, 1H), 7.63 (d, 1H), 7.53 (t, 1H), 7.38 (dd, 1H), 7.32-7.22 (m, 4H), 7.18 (d, 1H), 6.69 (s, 4H), 3.69 (s, 2H), 2.99 (t, 4H), 2.67 (br, 4H), 2.36 (s, 3H), 2.29 (s, 6H), 2.27 (s, 3H).

B208: (E)-1-(3-Dimethylaminomethyl-4-hydroxy-phenyl)-3-[2'-methyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone

10 General Procedure I gave the fumaric acid salt of the title product as yellow crystals in 38% yield. ¹H-NMR (DMSO-d₆): δ 8.08 (d, 1H), 8.04 (d, 1H), 8.03 (dd, 1H), 7.89, (s, 1H), 7.86 (d, 1H), 7.36 (dd, 1H), 7.32-7.24 (m, 4H), 7.19 (d, 1H), 6.90 (d, 1H), 6.58 (s, 2H), 3.85 (s, 2H), 2.99 (t, 4H), 2.67 (br, 4H), 2.39 (s, 6H), 2.36 (s, 3H), 2.26 (s, 3H).

B209: (E)-1-(4-Hydroxy-phenyl)-3-[2'-methyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone

General Procedure I gave the title product as yellow crystals in 40% yield. ¹H-NMR (DMSO-d₆): δ 10.38 (br, 1H), 8.07 (dt, 2H), 8.04 (d, 1H), 7.92 (d, 1H), 7.87 (d, 1H), 7.35 (dd, 1H), 7.32-7.24 (m, 4H), 7.17 (d, 1H), 6.86 (dt, 2H), 2.96 (t, 4H), 2.54 (br, 4H), 2.28 (s, 3H), 2.27 (s, 3H).

B210: (E)-1-(2-Fluoro-4-methoxy-phenyl)-3-[2'-methyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone

General Procedure I gave the fumaric acid salt of the title product as yellow crystals in 23% yield. ¹H-NMR (DMSO-d₆): δ 7.85 (d, 1H), 7.63 (d, 1H), 7.63 (d, 1H), 7.58 (d, 1H), 7.36 (dd, 1H), 7.31-7.21 (m, 5H), 7.18 (d, 1H), 6.65-6.63 (m, 1H), 6.60 (s, 4H), 3.83 (s, 3H), 2.99 (t, 4H), 2.65 (br, 4H), 2.37 (s, 3H), 2.26 (s, 3H).

B211: 2-Dimethylamino-N-(3-{3-[2'-methyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-(E)-acryloyl}-phenyl)-acetamide

General Procedure I gave the fumaric acid salt of the title product as yellow crystals in 3% yield. ¹H-NMR (DMSO-d₆): δ 9.93 (s, 1H), 8.30 (t, 1H), 8.08 (d, 1H), 7.98 (dd, 1H), 7.90-7.84 (m, 3H), 7.81 (d, 1H), 7.48 (t, 1H), 7.39 (dd, 1H), 7.31-7.24 (m, 3H), 7.20 (d, 1H), 6.60 (s, 6H), 3.14 (s, 2H), 2.99 (t, 4H), 2.61 (br, 4H), 2.33 (s, 3H), 2.31 (s, 6H), 2.26 (s, 3H).

B212: (E)-1-(3-Dimethylaminomethyl-4-methoxy-phenyl)-3-[2'-methyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone

General Procedure I gave the fumaric acid salt of the title product as yellow crystals in 16% yield. ¹H-NMR (DMSO-d₆): δ 8.23 (dd, 1H), 8.13 (d, 1H), 8.07 (d, 1H), 7.89 (d, 1H), 7.88 (d, 1H), 7.37 (dd, 1H), 7.32-7.25 (m, 4H), 7.20 (d, 1H), 7.15 (d, 1H), 6.58 (s, 4H), 3.90 (s, 3H), 3.75 (s, 3H), 3.01 (br t, 4H), 2.66 (br, 4H), 2.37 (s, 6H), 2.35 (s, 3H), 2.27 (s, 3H).

B213: (E)-1-(2-Dimethylaminomethyl-phenyl)-3-[2'-methoxy-3-(4-methyl-[1,4]diazepan-1-yl)-biphenyl-4-yl]-propenone

General Procedure I gave the fumaric acid salt of the title product as orange crystals in 82% yield. ¹H-NMR (DMSO-d₆): δ 7.82 (d, 1H), 7.62 (d, 1H), 7.50-7.41 (m, 4H), 7.39-7.31 (m, 2H), 7.25-7.20 (m, 2H), 7.14-7.00 (m, 3H), 6.57 (s, 3H), 3.77 (s, 3H), 3.54 (s, 2H), 3.25 (br, 2H), 3.07 (t, 2H), 2.77 (br, 4H), 2.44 (s, 3H), 2.09 (s, 6H), 1.81 (p, 2H).

B214: (E)-1-(3-Dimethylaminomethyl-phenyl)-3-[2'-methoxy-3-(4-methyl-[1,4]diazepan-1-yl)-biphenyl-4-yl]-propenone

General Procedure I gave the fumaric acid salt of the title product as orange crystals in 39% yield. ¹H-NMR (DMSO-d₆): δ 8.10 (d, 1H), 8.10-8.06 (m, 2H), 7.96 (d, 1H), 7.80 (d, 1H), 7.63 (br d, 1H), 7.56 (br t, 1H), 7.40-7.33 (m, 2H), 7.28 (d, 1H), 7.23 (dd, 1H), 7.13 (dd, 1H), 7.05 (td, 1H), 5.56 (s, 4H), 3.79 (s, 3H), 3.67 (s, 2H), 3.40 (br, 2H), 3.25 (t, 2H), 3.09 (br, 4H), 2.59 (s, 3H), 2.28 (s, 6H), 2.01 (p, 2H).

B215: (E)-3-[2'-Methoxy-3-(4-methyl-piperazin-1-yl)-biphenyl-4-yl]-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

General Procedure I gave the title product as yellow oil in 64% yield. ¹H-NMR (DMSO-d₆): δ 7.81 (d, 1H), 7.50 (d, 1H), 7.46-7.31 (m, 6H), 7.23 (dd, 1H), 7.14 (d, 1H), 7.11 (dd, 1H), 7.05 (d, 1H), 7.03 (td, 1H), 3.77 (s, 3H), 3.50 (s, 2H), 2.83 (t, 4H), 2.25 (br, 8H), 2.14 (br, 5H).

B216 : (E)-1-(2-[(2-Dimethylamino-ethyl)-methyl-amino]-methyl)-phenyl)-3-[2'-methoxy-3-(4-methyl-piperazin-1-yl)-biphenyl-4-yl]-propenone

General Procedure I gave the title product as yellow oil in 52% yield. ¹H-NMR (DMSO-d₆): δ 7.81 (d, 1H), 7.52 (d, 1H), 7.46-7.43 (m, 2H), 7.40-7.30 (m, 4H), 7.22 (dd, 1H), 7.14 (d, 1H), 7.11 (d, 1H), 7.05 (d, 1H), 7.04 (td, 1H), 3.76 (s, 3H), 3.54 (s, 2H), 2.83 (t, 4H), 2.35-2.18 (m, 8H), 2.14 (s, 3H), 2.01 (s, 9H).

B217 : (E)-1-{2-[(tert-Butyl-methyl-amino)-methyl]-phenyl}-3-[2'-methoxy-3-(4-methyl-piperazin-1-yl)-biphenyl-4-yl]-propenone

General Procedure I gave the title product as yellow crystals in 21% yield. ¹H-NMR (DMSO-d₆): δ 7.78 (d, 1H), 7.54 (d, 1H), 7.49 (d, 1H), 7.42 (td, 1H), 7.37-7.28 (m, 4H), 7.22 (d, 1H), 7.16-6.98 (m, 4H), 3.76 (s, 3H), 3.59 (s, 2H), 2.82 (br, 4H), 2.23 (br, 4H), 2.13 (s, 3H), 1.86 (s, 3H), 0.98 (s, 9H).

B218: (E)-1-(2-Dimethylaminomethyl-phenyl)-3-[5-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone

General Procedure I gave the fumaric acid salt of the title product as yellow crystals in 48% yield. ¹H NMR (DMSO-d₆): δ 7.74-7.71 (m, 2H), 7.54-7.27 (m, 11H), 7.22 (t, 1H), 6.60 (s, 4H), 3.63 (s, 2H), 3.22 (t, 4H), 2.59 (t, 4H), 2.32 (s, 3H), 2.13 (s, 6H).

Determination of metabolic stability

Incubations were performed with Wistar rat liver microsomes (0.25 mg/ml) in 2% sodium bicarbonate solution. NADP (0.13 mg/ml), glucose-6-phosphate (0.63 mg/ml) and glucose-6-phosphate dehydrogenase (0.38 units/ml) were used as NADPH generation system and UDPGA (0.48 mg/ml) was added to include the phase II reaction, glucuronic acid conjugation, in the assay. After 5 minutes of pre-incubation the reaction was started by addition of the test article to give a final concentration of 20 µM. Samples were incubated for 15 min at 37°C and the reactions were terminated by addition of equal volumes of acetonitrile. Blank incubations were performed at the same concentration but without addition of microsomes. Both blank and microsome-containing samples were made in replicats of three. Prior to analysis samples were centrifuged for 10 min. at 3500 rpm, HPLC system:

The fraction of compound metabolised during the 15 min of incubation was determined by comparison of blank and microsome-containing samples using a Waters Alliance 2690 separation module and Waters 996 PDA-detector (Waters, Milford, MA, USA.) Separation was performed on a XTerra MS C₁₈ column (150*2.1 mm I.D., 3,5 µm particle size) (Waters Milford, MA, USA) by. Initial conditions were 40% mobile phase A (acetonitrile) and 60% mobile phase B (10 mM ammonium acetate pH 9.5). During the first 20 minutes, the mobile phase was changed via a linear gradient to 90% A and 10% B. This was followed by a 5 minutes linear gradient to initial conditions, which were maintained for 5 min. The flow rate was 0.20 ml/min and injection volume 10 µl.

Determination of solubility

Solubility of the compounds was determined by preparing a saturated solution of compound in 0.3 M phosphate buffer (pH 7.4 ± 0.3) in a brown glass tube. The suspensions were rotated slowly for 24 hours. Aliquots were centrifuged for 10 minutes at 14.000 rpm and supernatants were diluted in 40% (v/v) acetonitrile in water prior to HPLC analysis. Concentrations of analytes were quantified against a standard curve and used as term of solubility.

The HPLC-UV method used for the assessment of solubility is the same as used in the *in vitro* metabolism assay.

Pharmacokinetic Studies

Evaluation of the pharmacokinetic properties of the compounds was done using female NMRI mice (weighing app. 30 g). Test articles were administrated intravenously and orally as a cassette dose formulation containing three compounds or as individual compounds. Samples of serum were taken at defined timepoints.

Standards and QC-samples in plasma were prepared and the serum concentrations of the test compounds quantified by HPLC-MS.

Prior to analysis, proteins were precipitated by deluding the samples (1:1) (v/v) with 100 % acetonitrile followed by centrifugation at 14.000 rpm in 10 min. The supernatant was used for the analysis.

5 HPLC-MS system:

A Waters Alliance HPLC-system (Milford, MA, USA) was coupled to a Quatro Micro triple quadrop mass spectrometer (Micromass, Manchester, UK) operating in positive (ESI) mode. Separation was performed on a XTerra MS C₁₈ column (150*2.1 mm I.D., 3,5 µm particle size) (Waters Milford, MA, USA).

- 10 Mobile phase A: 0.1% (v/v) formic acid or 10 mM ammonium acetate pH-adjusted to 9.5 in MilliQ-water, mobile phase B: 100% methanol. The gradient was as follows: 0 min = 70%A – 30% B, 0-10 min. a linear gradient to 10% A and 90 % B this was maintained till 11 min, 11-13 linear gradient to 70% A and 30% B this was maintained till 18 min. The flow rate was 0.20 ml/min, injection volume 10 µl.

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Biological testing

General methods

***In vitro* microbiological testing**

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MIC determination in broth microdilution assay

- Compounds were screened for activity against a panel of 10 different non-fastidious bacteria growing aerobically (*Staphylococcus aureus* ATCC29213; *Staphylococcus aureus* ATCC33591; *Staphylococcus intermedius* #2357 (clinical isolate from the Copenhagen area); *Enterococcus faecalis* ATCC29212; *Enterococcus faecium* #17501 (vancomycin-resistant clinical isolate); *Streptococcus pneumoniae* #998 (clinical isolate); *Streptococcus pyogenes* #14813 (clinical isolate); *Streptococcus agalactiae* #19855 (clinical isolate); *Eschericia coli* ATCC25922 and *Eschericia coli* ESS). The screening assay was done in 200 µl MH-broth cultures in microtitre plates. For compounds exhibiting activity in the initial screen MIC was determined in a microdilution assay using MH-broth as described by NCCLS (National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard – Fifth Edition. M7-A5 NCCLS 2000) modified to include uninoculated dilution series of test compounds to facilitate MIC determination if the test compound should precipitate. MIC was determined as the lowest concentration of test compound able to inhibit visible growth of bacteria. MICs for ATCC type strains fell within the limits posted by the NCCLS (National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Susceptibility Testing; Eleventh Informational Supplement. M100-S11 NCCLS 2001) when tested against vancomycin, tetracycline, gentamycin.

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MIC and MBC determination in broth macrodilution assay

MIC and MBC of test compounds were determined in a broth macrodilution assay using 2 ml MH-broth cultures and an inoculum of approximately 5×10^5 CFU/ml as described by Amsterdam (Amsterdam, D. Susceptibility testing of antimicrobials in liquid media. In V.Lorian (ed.): Antibiotics in Laboratory Medicine 4. edition. Williams & Wilkins 1996). MIC was determined as the minimal concentration of test compound able to inhibit visible growth of bacteria. Samples from cultures inhibited by test compound were plated onto unselective blood agar plates. MBC was determined as the minimal concentration of test compound able to decrease colony count on these plates below 0.1% compared to the original inoculum.

Killing Curve determination

For the determination of the killing curve of a test compound a dilution series of test compound was made and inoculated with approximately 5×10^5 CFU/ml as described for the MIC macrodilution assay above. At the timepoints indicated 100 μ l samples were withdrawn from the test tubes, serially diluted and spotted in duplicate on unselective agar plates to determine CFU. Test compounds with bactericidal activity are capable of decreasing surviving colony counts (CFU/ml) when incubated with bacteria. Bactericidal activity may be either primarily dependent on concentration of test compound or on incubation time with test compound. An example of a bactericidal compound (B143), which is primarily dependent on the concentration of the test compound is shown in Figure 4. An example of a bactericidal compound (B041) which is primarily dependent on the incubation time with the compound is shown in Figure 5.

MIC determination against Helicobacter pylori

Six strains of *Helicobacter pylori* were used in an agar dilution assay according to the standards of NCCLS (National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard – Fifth Edition. M7-A5 NCCLS 2000). MH-agar plates supplemented with 5% horse blood and containing a dilution series of the test compound were inoculated in duplicate with 10 μ l spots of a 2 McF suspension of the different strains of *H.pylori*. This inoculum corresponds to approximately 10^6 CFU/spot. Plates were then incubated in a microaerophilic atmosphere at 35°C for 72 hours. The MIC endpoint was determined as the lowest concentration of test compound able to completely inhibit or most significantly reduce growth compared to growth control plates not containing test compounds.

Activity determination against anaerobic bacteria

Screening for activity against anaerobic bacteria was done against two isolates of *Bacteroides fragilis*, an isolate of *Clostridium difficile* and an isolate of *Clostridium perfringens* in an agar dilution assay as described by NCCLS (National Committee for Clinical Laboratory Standards. Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard – Fifth Edition. M11-A5 NCCLS 2000) with the exception that

Mueller-Hinton agar was used in place of supplemented Brucella broth. Plates containing test compound at a single concentration (either 100 or 150 μ M) were prepared in duplicate along with appropriate control plates. Activity was present if growth in the presence of test substance was absent or most significantly reduced compared to growth control plates not
5 containing test compound.

Leishmania promastigote assay

A WHO reference vaccine strain of *L. major* originally isolated from a patient in Iran were cultured in Medium 199 with Hanks' Salts containing 0.02 mg/ml gentamycin, 25 mM
10 HEPES, 4 mM L-glutamine, and 10% heat inactivated fetal calf serum (FCS). Incubation was carried out at 27°C. Promastigotes were harvested at day 3 of culture and used for the assay of inhibition of parasite growth.

The effect of test compounds on promastigotes was assessed by a method modified from
15 Pearson et al. Briefly, promastigotes (0.8×10^6 /well) were incubated in 200 μ l duplicate cultures either with a dilution series of test compound or medium alone in 96 wells flat bottom microtiter plates. After 2h of incubation, 1.5 μ Ci of 3H-thymidine was added to each well and further incubated for 18 hours. The cultures were then harvested on Unifilter-GF/C microtiter filter plates (Packard Instruments), washed extensively and
20 counted in a TopCount-NXT microplate scintillation counter (Packard Instruments).

Plasmodium falciparum assay

Plasmodium falciparum 3D7 was maintained in culture by a modification of the method originally described by Trager and Jensen. In brief, the parasites were grown in
25 suspensions of human blood group O erythrocytes (RBC) maintained in RPMI1640 medium supplemented with 4.5 g/l Albumax II (Invitrogen), 10 mM hypoxanthine, 1.4 mM L-glutamine and 0.05 mg/ml gentamicin. Cultures were incubated at 37°C in atmosphere of 92.5% nitrogen, 5.5% carbon dioxide, and 2% oxygen. To obtain synchronized cultures of parasites erythrocytes infected with late trophozoite and schizont stages were separated
30 from ring stages and uninfected RBC by magnet-activated cell sorting (MACS; Miltenyi BioTec) (Staalsoe, T., H.A. Giha, D. Dodoo, T.G. Theander, and L. Hviid. 1999. Detection of antibodies to variant antigens on *Plasmodium falciparum*-infected erythrocytes by flow cytometry. Cytometry 35:329-336). Because of their high content of paramagnetic haemozoin, erythrocytes infected with late developmental stages of malaria parasites are
35 specifically retained within the column. The column was washed with PBS supplemented with 2% foetal calf serum and then the column was removed from the magnet and the retained late developmental stages of parasites were eluted and cultured for an additional 18 hours. At this time the culture is highly synchronous containing more than 90% ring stages.

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These synchronized cultures of ring stage parasites were used to assay for antimalarial parasites. Briefly, cultures of ring stage parasites were adjusted to 1% parasitemia by addition of uninfected RBC. Then, these were incubated in 125 μ l duplicate cultures

containing 2.5×10^7 RBC/well with either a dilution series of test compound or with medium alone. Plates were then incubated at 37°C for 24 hours when cultures were labelled by the addition 1.1 μ Ci 3H-phenylalanine and incubated overnight. Then, the cultures were harvested on Unifilter-GF/C microfilter plates (Packard Instruments) and washed
 5 extensively with water followed by a wash with 10% H₂O₂ to bleach hemoglobin. Filter plates were counted in a TopCount-NXT microplate scintillation counter (Packard Instruments).

DHODH Assay

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100 μ l chalcone or 0.1 M Tris-HCl pH 8.0 is added to a well in a 96-wells microtiter plate. Then 50 μ l enzyme dilution is added. The microtiter plate is placed in the Powerwave_x340 and the enzymatic reactions starts when adding 100 μ l assay mixture. The reaction are measured every 20 sec. for 10 min. The samples with chalcones are compared with the
 15 samples with 0.1 M Tris-HCl pH 8.0 and the percent inhibition is calculated.

Enzyme dilution: The solution of recombinant purified enzyme is dissolved in 0.1 M Tris-HCl pH 8 to give an initial velocity of 0.04 - 0.05 ΔA /min.

2,6-dichlorophenolindophenol (DCIP)-stock solution: 40 mg DCIP and 10 ml 99 % Ethanol are mixed for 10 min at RT. Then 100 μ l 1.0 M Tris-HCl pH 8 and milliQ H₂O are added to a

20 final volume of 100 ml. The A₆₀₀ of the DCIP-stock solution are measured in a microtiter plate on the Powerwave_x340 (Bio-Tek instruments, Inc.)

Dihydroorotate dehydrogenase (DHODH)-stock solution: 25 mM dihydroorotate stock-solution is prepared by first dissolving in the same amount of mol NaOH and then milliQ H₂O is added to the final volume.

25 Assay mix (10 ml solution): 600 μ l of DHODH-stock solution and X ml (depending on the A₆₀₀ value of stock-solution) DCIP to a final A₆₀₀ = 2.5 are mixed. Then 0.1 M Tris-HCl pH 8.0 are added to a final volume of 10 ml.

Preparation of compound solution: A 10 mM stock-solution of compound (e.g. a chalcone derivative) is made in dimethylsulfoxid (DMSO). The compound is then diluted in 0.1 M

30 Tris-HCl pH 8 to the test concentrations. The final DMSO concentration in the sample is 10%

In vivo models

35 *Effect of Chalcones Following Multiple Intra venous Administration in Plasmodium berghei K173 Infected NMRI Female Mice.*

Animals in groups of 6 were inoculated intra peritoneally with 1×10^6 infected red blood cells (RBC). On day 4 after infection, when the parasitaemia was 2-5%, treatment was
 40 initiated and the animals were dosed, according to the body weight recorded, once daily for 3 consecutive days (day 4-7). The doses stated were administered intra venously as solutions in a suitable vehicle. Parasitaemia, as percentage infected blood cells, was determined by counting 500 RBCs in stained (Giemsa) blood smears, prepared from blood samples from the tail vein taken on day 4 to 9 after infection.

45

Effect of Chalcones Following Multiple Oral Administrations in Plasmodium berghei K173 Infected NMRI Female Mice.

Animals in groups of 4 were inoculated intra peritoneally with 1×10^6 infected red blood cells (RBC). 2 hours after infection, treatment was initiated and the animals were dosed, according to the body weight recorded, twice daily for 3 consecutive days (day 0-3). The doses stated were administered orally as solutions in a suitable vehicle. Parasitaemia, as percentage infected blood cells, was determined by counting 500 RBCs in stained (Giemsa) blood smears, prepared from blood samples from the tail vein taken on day 6 after infection.

Treatment of leishmania donovani infected mice.

On Day -7 the animals (BALB/c female mice, app. 20 g, app. 8 weeks of age) were infected with the *L. donovani* amastigotes (ATCC 50127) collected from the spleen of a heavily infected donor mouse. Each mouse was inoculated intravenously in the tail vein with 1.5×10^7 amastigotes in 0.2 ml inoculation solution.

In order to check that the infection had been established before treatment was initiated the mice in Group 1 was sacrificed. The liver and spleen were removed and the infection load assessed in Giemsa-stained spleen impression smears using Stauber method (J. Protozool. 5(4), 269-273, 1958). The results were expressed as Leishmania Donovan Units (LDU): (Mean number of amastigotes per liver or spleen cell) x (mg liver or spleen).

The animals of Group 2 was left untreated until they were sacrificed on day 7, and the animals of Group 3 were treated with a saline solution. Groups 5 and 6 were administered B208 (10 mg/kg and 20 mg/kg) and group 4 were given Pentostam® (45 mg/kg)

Treatment of animals in Groups 3, 4, 5 and 6 occurred once daily on five consecutive (Days 0-4).

The compounds were administered intravenously (Groups 3, 5, and 6) or subcutaneously (Group 4). The dosing volume being 10 ml/kg for all treated groups. The animals in Groups 2, 3, 4, 5 and 6, were sacrificed on Day 7 and the infection load was assessed as previously described.

Biological Results

Licochalcone A (LicA) and 4'-methoxy chalcone (4'MC) described in WO 93/17671 are used as reference compounds in the following discussion.

Activity against non-fastidious bacteria

Licochalcone A exhibit moderate bactericidal activity against common pathogenic Gram-positive non-fastidious bacteria including *Staphylococcus aureus*, *Enterococcus faecalis*, *Enterococcus faecium*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Streptococcus agalactiae*. Licochalcone A maintains its activity also against antibiotic resistant bacteria, e.g. *Staphylococcus aureus* ATCC33591 (resistant to methicillin) and

Enterococcus faecium #17051 (resistant to vancomycin). In contrast, Licochalcone A have only modest or no activity against the prototype pathogenic Gram-negative bacterium, *Eschericia coli*. 4'MC as a representative of non-hydroxyl chalcones exhibit no antibacterial effect at all.

5

In comparison with Licochalcone A, diaminochalcones retain the activity of Licochalcone A against pathogenic Gram-positive bacteria including antibiotic-resistant strains (cf. Table 1). The diaminochalcones exhibit increased potency against Gram-positive pathogens (e.g. B101, B102, B115). In contrast to Licochalcone A, diaminochalcones exhibit activity
10 against *Eschericia coli*. Thus, several diaminochalcones e.g. B116 exhibits high activity against *E.coli* ATCC25922 and against the general more susceptible ESS strain of *E.coli* (cf. Table 1). This indicates the potential use of diaminochalcones in the treatment of infections with Gram-negative bacteria.

15 In the treatment of severe infections in immunocompromised patients bactericidal action of a antibiotic is a necessity. As exemplified in Figures 4 and 5, diaminochalcones retain the bactericidal action of Licochalcone A. For some diaminochalcones the bactericidal action is predominantly dependent on the concentration of the compound (e.g. B143; cf. Figure 4); for others the bactericidal action is predominantly dependent on the time of incubation
20 with the compound (e.g. B041; cf. Figure 5). This knowledge is helpful when designing dosing regimens for *in vivo* efficacy trials.

Table 1. Comparasion of the effect of diamino-chalcones and Licochalcone/4'MC on bacteria; MIC values in μ M.

	A	B	C	D	E	F	G	H
LICA	37.5	37.5	37.5	37.5	37.5	75.0		300.0
4'-MC	NA	NA	NA	NA	NA	NA	NA	NA
B041	4.7	4.7	9.4	9.4	9.4	18.8		300.0
B083	4.7	9.4	9.4	18.8	9.4	37.5		9.4
B089	4.7	4.7	4.7	9.4	9.4	37.5		
B182	4.7	4.7	4.7	9.4	4.7	18.8		75
B101	4.7	4.7	9.4	4.7	4.7	4.7	9.4	4.7
B102	4.7	9.4	18.8	9.4	9.4	4.7	37.5	4.7
B115	4.7	4.7	4.7	4.7	4.7	9.4		9.4
B116	2.4	4.7	4.7	4.7	4.7	4.7	4.7	4.7
B117	4.7	4.7	9.4	4.7	4.7		18.8	4.7

25 **A:** *Staphylococcus aureus* ATCC29213; **B:** *Staphylococcus aureus* ATCC33591(resistant to methicillin); **C:** *Staphylococcus intermedius* #2357(clinical isolate from the Copenhagen area); **D:** *Enterococcus faecalis* ATCC29212; **E:** *Enterococcus faecium* #17501 (vancomycin-resistant clinical isolate); **F:** *Streptococcus pneumoniae* #998 (clinical isolate); **G:** *Eschericia coli* ATCC25922 and **H:** *Eschericia coli* ESS. NA: no activity.

30

Activity against *Helicobacter pylori*

- Colonization of the gastric mucosa with *Helicobacter pylori* is an important pathogenic determinant for the development of gastritis and peptic ulcer. Diaminochalcones exhibit
- 5 activity against *Helicobacter pylori*. Several diaminochalcones (e.g. B019, B029, B039, B048, B060, B061, B067, B073, B195, B102) exhibit MICs in the range between 25 μ M and 100 μ M when tested against a panel of six strains *Helicobacter pylori*, that includes strains resistant to metronidazole. Metronidazole is an antibiotic commonly included in treatment regimens designed to eradicate *Helicobacter* colonization for the treatment of peptic ulcer.
- 10 The activity of diaminochalcones against both metronidazole-resistant and sensitive *Helicobacter pylori* clearly indicates the potential use of these compounds in the treatment of *Helicobacter* infections.

Activity against anaerobic bacteria

- 15 Diaminochalcones have been assayed in a single concentration of compound (100 μ M) for activity against a panel of anaerobic bacteria containing common human pathogenic bacteria (*Bacteroides fragilis*, *Clostridium perfringens*, *Clostridium difficile*). Several diaminochalcones (e.g. B022, B033, B035, B038, B039, B041, B046, B060 and B073)
- 20 exhibit activity against all microorganisms within the test panel. This clearly indicates the potential use of diaminochalcones in treatment of infection caused by anaerobic bacteria.

Activity against protozoa:

- 25 Activity against *Plasmodium falciparum*

- Plasmodium falciparum* is a protozoan parasite transmitted by the mosquito, *Anopheles*, and causing malignant or severe malaria in humans. Licochalcone A exhibit activity against *Plasmodium falciparum* *in vitro* and protects mice from infection with *P.yoelii* and *P.berghei*
- 30 (Chen et al., 1994). Diaminochalcones exhibit activity *in vitro* against *Plasmodium falciparum* and several diaminochalcones exhibit improved potency compared to Licochalcone A (cf. Table 2 and Figure 6). Furthermore the compounds are potent against chloroquine resistant parasites as shown in Table 3. The results clearly indicate the potential use of diaminochalcones in the treatment of malaria.

35

Table 2 Activity against *Plasmodium falciparum* 3D7.

Comp.	LicA	4'MC	B074	B208	B209	B211	B158	B216	B118
IC ₅₀ (μ M)	6.4	40.0	0.6	0.4	0.3	0.7	0.2	0.2	0.2

Comp.	B119	B147	B124
IC ₅₀ (μ M)	0.2	0.6	0.3

Table 3. Activity against resistant strains of *Plasmodium falciparum*.

	<i>Plasmodium falciparum</i> IC ₅₀ (μM)			
	3D7(Cq-sen)	DD2 (Cq-res)	7G8(Cq-res)	K1(Cq-res)
B111	1.6	1.0	1.3	1.0
Chloroquine	0.13	1.0	1.09	>1.56

5 Activity against *Leishmania major*

Leishmania major is a protozoan parasite transmitted by the sandfly, *Phlebotomus*, and causing cutaneous leishmaniasis or kala-azar in humans. Licochalcone A exhibit activity against *Leishmania* parasites and has shown efficacy in experimental animal models of cutaneous and visceral *Leishmania* infection (Chen et al., 1994). Diaminochalcones exhibit activity *in vitro* against *Leishmania major* with significantly improved potency compared to Licochalcone A and 4'MC (cf. Table 4). The results clearly indicate the potential use of diaminochalcones in the treatment of *Leishmania* infection.

15

Table 4. Effect of diamino-chalcones on *L. major*.

Comp	LicA	4'MC	B096	B185	B183	B208	B022	B039	B059	B067	B083
IC ₅₀ (μM)	4.6	5.6	1.2	0.2	0.5	1.1	0.8	1.0	0.5	0.9	0.5

Inhibition of DHODH.

Several of the diamino-chalcones prepared are potent inhibitors of DHODH. The compounds are as potent as LicA and by far more potent than ordinary chalcones exemplified by 4'MC.

Table 5. Inhibition of DHODH.

Comp	LicA	4'MC	B002	B012	B015	B017	B018	B022	B029	B058
%	25	7%	18%	19%	25%	23%	22%	21%	21%	17%

25

Metabolism

The usefulness of chalcones as drug candidates have been limited by the metabolism of the compounds resulting in short half-lives *in vivo* (LicA: 100% turn-over *in vitro* and t_{1/2} = 10 min *in vivo*).

30

The introduction of a diamino group in the chalcone changes the metabolic properties; this is clear from Table 6 where the metabolic turn-over of a number of diamino-chalcones are compared to LicA. The diamino-chalcones prepared are expected to show low or no metabolism *in vivo* as the metabolic turn-over are between 0-10% (compared to 100%

35

turn-over for LicA). Consequently the half-life of a diamino-chalcone will be longer, reducing the dose needed for treatment.

Table 6. Metabolic turn-over in vitro (%).

Comp	LicA	B111	B113	B216	B101	B119	B074	B115	B185	B182
%	100	4%	4%	6%	3%	9%	0%	0%	0%	2%

5

Solubility

The solubility of the neutral chalcones described in WO 93/17671 was very low. A representative chalcone 4'-methoxy-chalcone has a solubility <0.05 mg/ml. A few
 10 chalcones have a higher solubility due to (metabolically unstable) hydroxyl groups in the molecule. LicA has a solubility of approximately 0.01 mg/ml.

The diamino-chalcones described in this application are by far superior having solubility numbers in mg/ml. Representative examples are shown in table 7.

15

Table 7. Solubility in aqueous buffer at pH 7.4.

Comp	B023	B056	B074	B148	B126	B114	B124	B111
Solubility mg/ml	30.6	3.2	15.4	3.3	8.3	4.3	2.0	3.1

The high aqueous solubility means that dissolution and hence absorption will be no problem. This will inevitably cause a dramatic reduction of the dose needed making the
 20 diamino-chalcones very useful as drug candidates.

Bioavailability

The bioavailability of the diamino chalcones in mice is in general very high (e.g. 50% for
 25 B098). As the mouse is a very fast metabolizer of the amino chalcones compared to rat and human (e.g. B119 mice: 75%; rat: 8.6%; human: in general lower than rat) the bioavailability in rat and man is expected to be even higher due to limited first pass metabolism.

30 In vivo results

A number of amino-chalcones significantly reduce parasitaemia in plasmodium infected mice as illustrated on figures 8 and 10. The compounds are superior to pentostam treatment for visceral leishmaniasis as illustrated on figure 9.

35

Conclusion

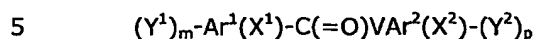
The use of chalcones as drug candidates for the treatment of parasitic or bacterial infections have been limited by the low in vivo potency (50mg/kg for LicA) of the compounds and a narrow spectrum of activity.

Several factors contribute to the low in vivo potency: Fast metabolism resulting in short half-lives in vivo; Low/no solubility in the intestine and consequently low/no absorption; Medium potency of the compounds against parasites and no activity against bacteria
5 (except for LicA).

The diamino-chalcones in this application are expected to fulfill the criteria for a drug candidate. The metabolism is low, the solubility is high and the compounds are potent against parasites as well as (resistant) Gram positive and Gram negative bacteria.

CLAIMS

1. A compound of the general formula



and salts thereof,

wherein Ar^1 and Ar^2 independently are selected from aryl and heteroaryl;

10

V designates $-CH_2-CH_2-$, $-CH=CH-$ or $-C\equiv C-$;

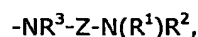
m is a whole number selected from the group consisting of 0, 1, and 2,

15 p is a whole number selected from the group consisting of 0, 1, and 2,

wherein the sum of m and p is at least 1;

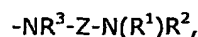
each Y^1 independently represents a diamino-functional substituent of the formula

20



each Y^2 independently represents a diamino-functional substituent of the formula

25



wherein Z is a biradical $-(C(R^H)_2)_n-$, wherein n is an integer in the range of 1-6 and each R^H is independently selected from hydrogen and C_{1-6} -alkyl, or wherein $(R^H)_2$ is $=O$;

30 R^1 and R^2 independently are selected from hydrogen, optionally substituted C_{1-12} -alkyl, optionally substituted C_{2-12} -alkenyl, optionally substituted C_{4-12} -alkadienyl, optionally substituted C_{6-12} -alkatrienyl, optionally substituted C_{2-12} -alkynyl, optionally substituted C_{1-12} -alkoxycarbonyl, optionally substituted C_{1-12} -alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroarylcarbonyl, aminocarbonyl, mono- and di(C_{1-6} -alkyl)aminocarbonyl, amino- C_{1-6} -alkyl-aminocarbonyl, mono- and di(C_{1-6} -alkyl)amino- C_{1-6} -alkyl-aminocarbonyl; wherein $N(R^1)R^2$ forms an optionally substituted nitrogen-containing heterocyclic ring; R^3 is selected from hydrogen, C_{1-6} -alkyl, and C_{1-6} -alkylcarbonyl, said alkyl and alkylcarbonyl optionally carrying substituent(s) selected from halogen, hydroxy, C_{1-6} -alkoxy, carboxy, C_{1-6} -alkoxycarbonyl, C_{1-6} -alkylcarbonyl, amino, mono- and di(C_{1-6} -alkyl)amino, and aryl optionally substituted 1-3 times with C_{1-4} -alkyl, C_{1-4} -alkoxy, nitro, cyano, amino or halogen; or R^1 and R^3 together form a biradical Z^* which is as defined for Z;

40

- X¹ and X² independently designates a substituent present 0-5 times, on Ar¹ and Ar², respectively, wherein each X¹ and X² is independently selected from the group consisting of optionally substituted C₁₋₁₂-alkyl, optionally substituted C₂₋₁₂-alkenyl, optionally substituted C₄₋₁₂-alkadienyl, optionally substituted C₆₋₁₂-alkatrienyl, optionally substituted C₂₋₁₂-alkynyl, hydroxy, optionally substituted C₁₋₁₂-alkoxy, optionally substituted C₂₋₁₂-alkenyloxy, carboxy, optionally substituted C₁₋₁₂-alkoxycarbonyl, optionally substituted C₁₋₁₂-alkylcarbonyl, formyl, C₁₋₆-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxy, optionally substituted aryloxy, optionally substituted arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroaryloxy, optionally substituted heteroarylcarbonyl, optionally substituted heteroarylamino, heteroarylsulphonylamino, optionally substituted heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylcarbonyl, optionally substituted heterocyclylamino, heterocyclylsulphonylamino, amino, mono- and di(C₁₋₆-alkyl)amino, carbamoyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-aminocarbonyl, C₁₋₆-alkylcarbonylamino, amino-C₁₋₆-alkyl-carbonylamino, mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-carbonylamino, cyano, guanidino, carbamido, C₁₋₆-alkanoyloxy, C₁₋₆-alkylsulphonyl, C₁₋₆-alkylsulphonyl, C₁₋₆-alkylsulphonyloxy, aminosulfonyl, mono- and di(C₁₋₆-alkyl)aminosulfonyl, nitro, optionally substituted C₁₋₆-alkylthio, and halogen, where any nitrogen-bound C₁₋₆-alkyl is optionally substituted with hydroxy, C₁₋₆-alkoxy, C₂₋₆-alkenyloxy, amino, mono- and di(C₁₋₆-alkyl)amino, carboxy, C₁₋₆-alkylcarbonylamino, halogen, C₁₋₆-alkylthio, C₁₋₆-alkyl-sulphonyl-amino, or guanidine.
2. The compound according to claim 1, wherein R¹ and R² independently are selected from hydrogen, optionally substituted C₁₋₁₂-alkyl, optionally substituted C₂₋₁₂-alkenyl, optionally substituted C₂₋₁₂-alkynyl, optionally substituted C₁₋₁₂-alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, aminocarbonyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, and mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-aminocarbonyl.
3. The compound according to any of the preceding claims, wherein R³ is selected from hydrogen and methyl, in particular methyl.
4. The compound according to any of the preceding claims, wherein X¹ and X² independently designates 0-4, such as 0-3, e.g. 0-2, substituents, where such optional substituents independently are selected from optionally substituted C₁₋₁₂-alkyl, hydroxy, optionally substituted C₁₋₁₂-alkoxy, optionally substituted C₂₋₁₂-alkenyloxy, carboxy, optionally substituted C₁₋₁₂-alkylcarbonyl, formyl, C₁₋₆-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxy, optionally substituted aryloxy, optionally substituted arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, optionally substituted heteroarylcarbonyl, optionally substituted heteroaryloxy, heteroarylsulphonylamino, optionally substituted heterocyclyl, optionally substituted

- heterocycloxy, optionally substituted heterocyclamino, amino, mono- and di(C₁₋₆-alkyl)amino, carbamoyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkylaminocarbonyl, mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkylaminocarbonyl, C₁₋₆-alkylcarbonylamino, amino-C₁₋₆-alkyl-carbonylamino, mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-
- 5 carbonylamino, guanidino, carbamido, C₁₋₆-alkylsulphonyl, C₁₋₆-alkylsulphinyl, C₁₋₆-alkylsulphonyloxy, optionally substituted C₁₋₆-alkylthio, aminosulfonyl, mono- and di(C₁₋₆-alkyl)aminosulfonyl, and halogen, where any nitrogen-bound C₁₋₆-alkyl may be substituted with a substituent selected from the group consisting of hydroxy, C₁₋₆-alkoxy, and halogen.
- 10 5. The compound according to any of the preceding claims, wherein R¹ and R² independently are selected from hydrogen, optionally substituted C₁₋₆-alkyl, optionally substituted C₁₋₆-alkylcarbonyl, heteroarylcarbonyl, aminocarbonyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkylaminocarbonyl, mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkylaminocarbonyl
- 15 6. The compound according to any of the preceding claims, wherein X¹ and X² independently designates 0-3, e.g. 0-2, substituents, where such optional substituents independently are selected from optionally substituted C₁₋₆-alkyl, hydroxy, optionally substituted C₁₋₆-alkoxy, carboxy, optionally substituted C₁₋₆-alkylcarbonyl, C₁₋₆-
- 20 alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, heteroarylsulphonylamino, amino, mono- and di(C₁₋₆-alkyl)amino, carbamoyl, C₁₋₆-alkylcarbonylamino, guanidino, carbamido, optionally substituted C₁₋₆-alkylthio, optionally substituted heterocyclyl, optionally substituted
- 25 heterocycloxy, optionally substituted heterocyclamino and halogen, where any nitrogen-bound C₁₋₆-alkyl may be substituted with a substituent selected from the group consisting of hydroxy, C₁₋₆-alkoxy, and halogen.
7. The compound according to any of the preceding claims, wherein V designates
- 30 -CH=CH-.
8. The compound according to any of the preceding claims, wherein at least one of Ar¹ and Ar², preferably both, are phenyl.
- 35 9. The compound according to claim 8, wherein both of Ar¹ and Ar² are phenyl, m is 1 or 2, and p is 0.
10. The compound according to any of the preceding claims, wherein X² represents at least one substituent selected from C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylcarbonyl, optionally
- 40 substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, mono- and di(C₁₋₆-alkyl)amino, C₁₋₆-alkylcarbonylamino, optionally substituted C₁₋₆-alkylthio, optionally substituted heterocyclyl, optionally substituted heterocycloxy, optionally substituted heterocyclamino and halogen.

11. The compound according to any of the preceding claims, wherein X^2 represents at least two halogen atoms.

5 12. The compound according to any of claims 1-8 and 10-11, wherein at least one or Ar^1 and Ar^2 is selected from the group consisting of thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, quinolyl, isoquinolyl, and indolyl.

13. The compound according to any of the preceding claims, wherein Z is $-(CH_2)_n-$, wherein
10 n is 2-4, such as 2-3.

14. The compound according to any of the preceding claims, wherein one of Y^1 and Y^2 represents a substituent of the formula

15 $-NR^3-(CH_2)_{2-3}-N(R^1)R^2$

wherein R^3 is selected from hydrogen and methyl, and R^1 and R^2 are selected from hydrogen and C_{1-6} -alkyl.

20 15. The compound according to claim 14, wherein V is $-CH=CH-$, and Ar^1 and Ar^2 both are phenyl.

16. The compound according to claim 1, selected from the group consisting of:

25 3-[5-Bromo-2-(4-methyl-piperazin-1-yl)-phenyl]-1-(2-fluoro-4-methoxy-phenyl)-propenone,
3-(2,4-Dichlorophenyl)-1-(4-fluorophenyl)propan-1-one,
3-[3-(2-Dimethylamino-ethylamino)-phenyl]-1-(4-methoxy-phenyl)-propenone,
3-(2,4-Dichloro-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-
30 propenone,
1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(4-fluoro-phenyl)-propenone,
3-(2,5-Difluoro-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone,
3-(2-Bromo-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone,
35 3-(4-Bromo-2-fluoro-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone,
3-[4-(2-Dimethylamino-ethylamino)-phenyl]-1-(4-methoxy-phenyl)-propenone,
3-(4-Chloro-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone,
3-(3-Bromo-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone,
40 4-(3-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-oxo-propenyl)-benzonitrile,
3-(2,5-Dimethoxy-phenyl)-1-[4-(3-dimethylamino-propylamino)-phenyl]-propenone,
3-(2,4-Dichloro-phenyl)-1-[4-(3-dimethylamino-propylamino)-phenyl]-propenone,
3-[4-(2-Dimethylamino-ethylamino)-phenyl]-1-(2,3,4-trimethoxy-phenyl)-propenone,
3-[4-(2-Dimethylamino-ethylamino)-phenyl]-1-(2-fluoro-4-methoxy-phenyl)-propenone,

- 3-(2,4-Dichloro-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone,
3-(4-Chloro-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone,
3-(2,5-Difluoro-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-
5 propenone,
3-(4-Bromo-2-fluoro-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone,
3-(2-Chloro-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone,
1-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(4-methoxy-phenyl)-propenone,
10 3-(2,4-Dimethoxy-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone,
3-(2,4-Dichloro-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone,
1-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(4-methoxy-phenyl)-propenone,
1-(2,3-Dichloro-phenyl)-3-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone,
15 3-(4-Chloro-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone,
3-(2,4-Dimethoxy-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone,
1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(4-methoxy-phenyl)-propenone,
3-(2,5-Dimethoxy-phenyl)-1-[2-(2-dimethylamino-ethylamino)-phenyl]-propenone,
3-(2,4-Dichloro-phenyl)-1-[2-(2-dimethylamino-ethylamino)-phenyl]-propenone,
20 1-[4-(3-Dimethylamino-propylamino)-phenyl]-3-(4-fluoro-phenyl)-propenone,
3-(2,5-Dimethoxy-phenyl)-1-[2-(3-dimethylamino-propylamino)-phenyl]-propenone,
3-(2,5-Dimethoxy-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone,
3-(3-Dibutylamino-phenyl)-1-[2-(3-dimethylamino-propylamino)-phenyl]-propenone,
25 1-[2-(3-Dimethylamino-propylamino)-phenyl]-3-(3-dipropylamino-phenyl)-propenone,
1-[2-(2-Dimethylamino-ethylamino)-phenyl]-3-(3-dipropylamino-phenyl)-propenone,
3-(2,4-Dimethoxy-phenyl)-1-[2-(3-dimethylamino-propylamino)-phenyl]-propenone,
3-(2,4-Dimethoxy-phenyl)-1-[2-(2-dimethylamino-ethylamino)-phenyl]-propenone,
3-(5-Dibutylamino-2-methoxy-phenyl)-1-[2-(2-dimethylamino-ethylamino)-phenyl]-
30 propenone,
3-(2,4-Dichloro-phenyl)-1-[3-(2-dimethylamino-ethylamino)-phenyl]-propenone,
3-[5-(1,1-Dimethyl-allyl)-2-methoxy-phenyl]-1-[4-(3-dimethylamino-propylamino)-phenyl]-propenone,
3-(3-Dibutylamino-phenyl)-1-[2-(2-dimethylamino-ethylamino)-phenyl]-propenone,
35 3-(2,4-Dimethoxy-phenyl)-1-[3-(2-dimethylamino-ethylamino)-phenyl]-propenone,
3-(2,5-Dimethoxy-phenyl)-1-[3-(2-dimethylamino-ethylamino)-phenyl]-propenone,
3-(2,4-Dimethoxy-phenyl)-1-{2-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone,
3-(2,5-Dimethoxy-phenyl)-1-{2-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-
40 propenone,
3-(3,5-Bis-trifluoromethyl-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone,
3-(3,5-Dimethoxy-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone,

- 1-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-phenyl-propenone,
3-(4-Diethylaminomethyl-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-
propenone,
3-(3,5-Dimethoxy-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone,
5 1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-phenyl-propenone,
3-(4-Diethylaminomethyl-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone,
1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(2-fluoro-phenyl)-propenone,
1-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(2-fluoro-phenyl)-propenone,
3-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2,3,4-trimethoxy-phenyl)-
10 propenone,
3-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2-methoxy-phenyl)-propenone,
3-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2-dimethylaminomethyl-
phenyl)-propenone,
3-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2-fluoro-4-methoxy-phenyl)-
15 propenone,
1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(4-pyridin-2-yl-phenyl)-
propenone,
3-(4-Butyl-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone,
1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-quinolin-3-yl-propenone,
20 1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(4-pyridin-2-yl-phenyl)-propenone,
3-(4-Butyl-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone,
1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(4-methoxy-biphenyl-3-yl)-propenone,
3-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-[2-(4-methyl-piperazin-1-
ylmethyl)-phenyl]-propenone ,
25 1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-quinolin-3-yl-propenone,
1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-quinolin-2-yl-propenone,
1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(4-dimethylamino-phenyl)-propenone,
1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(4-imidazol-1-yl-phenyl)-propenone,
3-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-
30 propenone,
1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-{3-[(2-dimethylamino-ethyl)-methyl-
amino]-phenyl}-propenone,
1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(2-dimethylaminomethyl-phenyl)-
propenone,
35 1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(4-methoxy-biphenyl-3-yl)-
propenone,
3-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2-dimethylaminomethyl-
phenyl)-propenone,
1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(2-dimethylaminomethyl-phenyl)-
40 propenone,
3-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-[2-(4-methyl-piperazin-1-
ylmethyl)-phenyl]-propenone,
1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(2-dimethylaminomethyl-
phenyl)-propenone,

- 1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(4-imidazol-1-yl-phenyl)-propenone,
1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(4-phenoxy-phenyl)-propenone,
3-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2-dimethylaminomethyl-phenyl)-propenone,
5 1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(3-phenoxy-phenyl)-propenone,
1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(3-morpholin-4-ylmethyl-phenyl)-propenone,
1-(2-Fluoro-4-methoxy-phenyl)-3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-
10 propenone,
1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-[3-(pyridin-3-ylamino)-phenyl]-propenone,
3-(4-Diethylamino-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-
15 propenone,
1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-quinolin-2-yl-propenone,
N-{3-[3-(2,5-Dimethoxy-phenyl)-acryloyl]-phenyl}-2-dimethylamino-acetamide,
N-{3-[3-(4-Dibutylamino-phenyl)-acryloyl]-phenyl}-2-dimethylamino-acetamide,
3-(2,4-Dichlorophenyl)-1-{4-[(2-dimethylamino-ethyl)methylamino]phenyl}-propan-1-
20 one,
3-{3-[4-(2-Methoxy-acetyl)-piperazin-1-yl]-phenyl}-1-(4-methoxy-phenyl)-propenone,
N-{3-[3-(2,4-Dichloro-phenyl)-acryloyl]-phenyl}-2-dimethylamino-acetamide,
N-{3-[3-(4-Dibutylamino-phenyl)-acryloyl]-phenyl}-2-(4-methyl-piperazin-1-yl)-acetamide,
25 1-(3-Dimethylaminomethyl-phenyl)-3-[2'-methoxy-3-(4-methyl-piperazin-1-yl)-biphenyl-4-yl]-propenone,
1-(2-Dimethylaminomethyl-phenyl)-3-[2'-methoxy-3-(4-methyl-piperazin-1-yl)-biphenyl-4-yl]-propenone,
N-{4-[3-(2,4-Dichloro-phenyl)-acryloyl]-phenyl}-*N*-(2-dimethylamino-ethyl)-acetamide,
30 1-(3-Dimethylaminomethyl-4-hydroxy-phenyl)-3-[2'-methoxy-3-(4-methyl-piperazin-1-yl)-biphenyl-4-yl]-propenone,
1-(2-Dimethylaminomethyl-4-methoxy-phenyl)-3-[6-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
1-(3-Dimethylaminomethyl-4-methoxy-phenyl)-3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
35 1-[3-(2-Dimethylamino-ethylamino)-phenyl]-3-[3',5'-dimethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
1-(2-Dimethylaminomethyl-4-methoxy-phenyl)-3-[3',5'-dimethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
40 1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-{3-[4-(2-methoxy-acetyl)-piperazin-1-yl]-phenyl}-propenone,
3-{3-[4-(2-Dimethylamino-acetyl)-piperazin-1-yl]-phenyl}-1-(3-dimethylaminomethyl-phenyl)-propenone,

- 3-{3-[4-(2-Dimethylamino-acetyl)-piperazin-1-yl]-phenyl}-1-(2-fluoro-4-methoxy-phenyl)-propenone,
1-(2-Fluoro-4-methoxy-phenyl)-3-[4-(4-methyl-piperazin-1-yl)-biphenyl-2-yl]-propenone,
1-[3-(2-Dimethylamino-ethylamino)-phenyl]-3-[4-(4-methyl-piperazin-1-yl)-biphenyl-2-yl]-propenone,
5 1-(4-Hydroxy-phenyl)-3-[4-(4-methyl-piperazin-1-yl)-biphenyl-2-yl]-propenone,
1-(3-Dimethylaminomethyl-phenyl)-3-[4-(4-methyl-piperazin-1-yl)-biphenyl-2-yl]-propenone,
1-(3-Dimethylaminomethyl-4-methoxy-phenyl)-3-[4-(4-methyl-piperazin-1-yl)-biphenyl-2-yl]-propenone,
10 1-(2-Dimethylaminomethyl-4-methoxy-phenyl)-3-[5-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
1-[3-(2-Dimethylamino-ethylamino)-phenyl]-3-[5-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
15 1-[3-(2-Dimethylamino-ethylamino)-phenyl]-3-{4-[(2-dimethylamino-ethyl)-methyl-amino]-3',5'-dimethyl-biphenyl-3-yl}-propenone,
3-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-3',5'-dimethyl-biphenyl-3-yl}-1-(2-dimethylaminomethyl-4-methoxy-phenyl)-propenone,
1-(2-Amino-phenyl)-3-[3',5'-dimethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
20 1-[3-(2-Dimethylamino-ethylamino)-phenyl]-3-(3',5'-dimethyl-4-piperazin-1-yl-biphenyl-3-yl)-propenone,
1-(2-Dimethylaminomethyl-4-methoxy-phenyl)-3-(3',5'-dimethyl-4-piperazin-1-yl-biphenyl-3-yl)-propenone,
25 3-{3-Bromo-5-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2-dimethylaminomethyl-phenyl)-propenone,
3-{5-[(2-Dimethylamino-ethyl)-methyl-amino]-2'-methyl-biphenyl-3-yl}-1-(2-dimethylaminomethyl-phenyl)-propenone,
3-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-2'-methyl-biphenyl-4-yl}-1-(2-dimethylaminomethyl-phenyl)-propenone,
30 3-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-2'-methyl-biphenyl-4-yl}-1-(3-dimethylaminomethyl-phenyl)-propenone,
3-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-2'-methyl-biphenyl-4-yl}-1-(3-dimethylaminomethyl-4-hydroxy-phenyl)-propenone,
35 3-[5-Bromo-2-(4-methyl-piperazin-1-yl)-phenyl]-1-(2-dimethylaminomethyl-phenyl)-propenone,
3-[2-Bromo-5-(4-methyl-piperazin-1-yl)-phenyl]-1-(2-dimethylaminomethyl-phenyl)-propenone,
3-{5-[(2-Dimethylamino-ethyl)-methyl-amino]-2'-methyl-biphenyl-3-yl}-1-(2-dimethylaminomethyl-4-methoxy-phenyl)-propenone,
40 3-[3-Bromo-5-(3-dimethylamino-propylamino)-phenyl]-1-(2-dimethylaminomethyl-phenyl)-propenone,
1-(2-Dimethylaminomethyl-4-methoxy-phenyl)-3-[5-(3-dimethylamino-propylamino)-2'-methyl-biphenyl-3-yl]-propenone,

- 1-(2-Dimethylaminomethyl-phenyl)-3-[2'-methyl-4-(4-methyl-piperazin-1-yl)-biphenyl-2-yl]-propenone,
1-(2-Dimethylaminomethyl-4-methoxy-phenyl)-3-[2'-methyl-4-(4-methyl-piperazin-1-yl)-biphenyl-2-yl]-propenone,
5 1-(2-Dimethylaminomethyl-phenyl)-3-[2'-methyl-5-(4-methyl-[1,4]diazepan-1-yl)-biphenyl-3-yl]-propenone,
1-(2-Dimethylaminomethyl-4-methoxy-phenyl)-3-[2'-methyl-5-(4-methyl-[1,4]diazepan-1-yl)-biphenyl-3-yl]-propenone,
1-(2-Dimethylaminomethyl-phenyl)-3-[2'-methyl-5-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
10 1-(2-Dimethylaminomethyl-4-methoxy-phenyl)-3-[2'-methyl-5-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
1-[3-(2-Dimethylamino-ethylamino)-phenyl]-3-{4-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-2'-methoxy-biphenyl-3-yl}-propenone,
15 1-(2-Fluoro-4-methoxy-phenyl)-3-{4-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-2'-methoxy-biphenyl-3-yl}-propenone,
1-[3-(2-Dimethylamino-ethylamino)-phenyl]-3-[4-(4-methyl-piperazin-1-yl)methyl]-biphenyl-3-yl]-propenone,
1-(2-Fluoro-4-methoxy-phenyl)-3-{2-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-phenyl}-propenone,
20 1-(2-Fluoro-4-methoxy-phenyl)-3-[2-(4-methyl-piperazin-1-yl)-5-pyridin-2-yl-phenyl]-propenone,
3-[4-Chloro-5-(1,1-dimethyl-allyl)-2-methoxy-phenyl]-1-[4-methoxy-2-(4-methyl-piperazin-1-yl)-phenyl]-propenone,
25 3-[2'-Methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-1-[4-methoxy-2-(4-methyl-piperazin-1-yl)-phenyl]-propenone,
3-[4-(4-Acetyl-piperazin-1-yl)-2'-methoxy-biphenyl-3-yl]-1-(2-fluoro-4-methoxy-phenyl)-propenone,
4-{4-Bromo-2-[3-(2-fluoro-4-methoxy-phenyl)-3-oxo-propenyl]-phenyl}-piperazine-1-carboxylic acid tert-butyl ester,
30 4-{3-[3-(2-Fluoro-4-methoxy-phenyl)-3-oxo-propenyl]-2'-methoxy-biphenyl-4-yl}-piperazine-1-carboxylic acid tert-butyl ester,
3-[5-Bromo-2-(4-methyl-[1,4]diazepan-1-yl)-phenyl]-1-(2-fluoro-4-methoxy-phenyl)-propenone,
35 1-(2-Fluoro-4-methoxy-phenyl)-3-[2'-methoxy-4-(4-methyl-[1,4]diazepan-1-yl)-biphenyl-3-yl]-propenone,
1-(2-Dimethylaminomethyl-phenyl)-3-[2'-methyl-4-(4-pyrrolidin-1-yl-piperidin-1-yl)-biphenyl-3-yl]-propenone,
1-(2-Dimethylaminomethyl-phenyl)-3-{2'-methyl-4-[methyl-(1-methyl-piperidin-4-yl)-amino]-biphenyl-3-yl}-propenone,
40 1-(2-Dimethylaminomethyl-phenyl)-3-{4-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-2'-methyl-biphenyl-3-yl}-propenone,
1-(2-Dimethylaminomethyl-phenyl)-3-{4-[(3-dimethylamino-propyl)-methyl-amino]-2'-methyl-biphenyl-3-yl}-propenone,

- 3-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-2'-methyl-biphenyl-3-yl}-1-(2-dimethylaminomethyl-phenyl)-propenone,
N-(2-{3-[3',5'-Dimethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-acryloyl}-phenyl)-benzenesulfonamide,
- 5 Propane-1-sulfonic acid (2-{3-[3',5'-dimethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-acryloyl}-phenyl)-amide,
N-(2-{3-[3',5'-Dimethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-acryloyl}-phenyl)-methanesulfonamide,
3-(5-tert-Butyl-2-methoxy-phenyl)-1-[2-fluoro-6-(4-methyl-piperazin-1-yl)-phenyl]-propenone,
- 10 3-[3',5'-Dimethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-1-[2-fluoro-6-(4-methyl-piperazin-1-yl)-phenyl]-propenone,
1-[2,6-Bis-(4-methyl-piperazin-1-yl)-phenyl]-3-(3-dibutylamino-phenyl)-propenone,
1-[2,4-Bis-(4-methyl-piperazin-1-yl)-phenyl]-3-(3-dibutylamino-phenyl)-propenone,
- 15 3-(3-Dibutylamino-phenyl)-1-[2-fluoro-6-(4-methyl-piperazin-1-yl)-phenyl]-propenone,
1-[2,4-Bis-(4-methyl-piperazin-1-yl)-phenyl]-3-[5-bromo-2-(4-methyl-piperazin-1-yl)-phenyl]-propenone,
1-[2,4-Bis-(4-methyl-piperazin-1-yl)-phenyl]-3-[3',5'-dimethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
- 20 1-[2,4-Bis-(4-methyl-piperazin-1-yl)-phenyl]-3-(5-tert-butyl-2-methoxy-phenyl)-propenone,
1-[2,4-Bis-(4-methyl-piperazin-1-yl)-phenyl]-3-(2,4-dichloro-phenyl)-propenone,
1-[2,4-Bis-(4-methyl-piperazin-1-yl)-phenyl]-3-(3-dimethylaminomethyl-phenyl)-propenone,
- 25 3-[3',5'-Dimethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-1-[2-(4-methyl-piperazin-1-yl)-phenyl]-propenone,
3-(2,4-Dichloro-phenyl)-1-[2-fluoro-6-(4-methyl-piperazin-1-yl)-phenyl]-propenone,
1-[2,4-Bis-(4-methyl-piperazin-1-yl)-phenyl]-3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
- 30 3-(3-Dimethylaminomethyl-phenyl)-1-[2-fluoro-6-(4-methyl-piperazin-1-yl)-phenyl]-propenone,
1-[2-Fluoro-6-(4-methyl-piperazin-1-yl)-phenyl]-3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
3-[5-Bromo-2-(4-methyl-piperazin-1-yl)-phenyl]-1-[2-(4-methyl-piperazin-1-yl)-phenyl]-propenone,
- 35 3-(5-tert-Butyl-2-methoxy-phenyl)-1-[2-(4-methyl-piperazin-1-yl)-phenyl]-propenone,
3-(3-Dibutylamino-phenyl)-1-[2-(4-methyl-piperazin-1-yl)-phenyl]-propenone,
3-(2,4-Dichloro-phenyl)-1-[2-(4-methyl-piperazin-1-yl)-phenyl]-propenone,
3-(3-Dimethylaminomethyl-phenyl)-1-[2-(4-methyl-piperazin-1-yl)-phenyl]-propenone,
- 40 3-[2'-Methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-1-[2-(4-methyl-piperazin-1-yl)-phenyl]-propenone,
3-(5-tert-Butyl-2-methoxy-phenyl)-1-[4-hydroxy-2-(4-methyl-piperazin-1-yl)-phenyl]-propenone,

- 3-(3,5-Di-tert-butyl-2-methoxy-phenyl)-1-[4-hydroxy-2-(4-methyl-piperazin-1-yl)-phenyl]-propenone,
1-(3-Fluoro-4-hydroxy-phenyl)-3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
- 5 1-(3-Dimethylaminomethyl-4-hydroxy-phenyl)-3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
2-Dimethylamino-N-(3-{3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-acryloyl}-phenyl)-acetamide,
1-(2,6-Difluoro-phenyl)-3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-
- 10 propenone,
1-(3-Fluoro-4-methoxy-phenyl)-3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
1-(2-Fluoro-4-methoxy-phenyl)-3-[4'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
- 15 1-(2-Fluoro-4-methoxy-phenyl)-3-[3'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
3-[3',5'-Dimethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-1-(2-fluoro-4-methoxy-phenyl)-propenone,
1-(2-Fluoro-4-methoxy-phenyl)-3-[2-(4-methyl-piperazin-1-yl)-5-pyridin-3-yl-phenyl]-
- 20 propenone,
1-(4-Hydroxy-phenyl)-3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
N-(2-{3-[2'-Methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-acryloyl}-phenyl)-benzenesulfonamide,
- 25 1-(2-Fluoro-4-hydroxy-phenyl)-3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
N-[3'-[3-(2-Fluoro-4-methoxy-phenyl)-3-oxo-propenyl]-4'-(4-methyl-piperazin-1-yl)-biphenyl-4-yl]-acetamide,
3'-[3-(2-Fluoro-4-methoxy-phenyl)-3-oxo-propenyl]-4'-(4-methyl-piperazin-1-yl)-
- 30 biphenyl-4-carboxylic acid,
3-[4'-Amino-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-1-(2-fluoro-4-methoxy-phenyl)-propenone,
1-(2-Fluoro-4-methoxy-phenyl)-3-[4'-methanesulfonyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
- 35 1-(2-Fluoro-4-methoxy-phenyl)-3-[3'-hydroxymethyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
1-(2-Fluoro-4-methoxy-phenyl)-3-[2-(4-methyl-piperazin-1-yl)-5-thiophen-3-yl-phenyl]-propenone,
1-(2-Fluoro-4-methoxy-phenyl)-3-[4'-hydroxymethyl-4-(4-methyl-piperazin-1-yl)-
- 40 biphenyl-3-yl]-propenone,
1-(2-Fluoro-4-methoxy-phenyl)-3-[4-(4-methyl-piperazin-1-yl)-4'-trifluoromethyl-biphenyl-3-yl]-propenone,
1-(2-Fluoro-4-methoxy-phenyl)-3-[2'-fluoro-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,

- 1-(2-Fluoro-4-methoxy-phenyl)-3-[4-(4-methyl-piperazin-1-yl)-3'-trifluoromethyl-biphenyl-3-yl]-propenone,
1-(2-Fluoro-4-methoxy-phenyl)-3-[4'-fluoro-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
5 1-(2-Fluoro-4-methoxy-phenyl)-3-[3'-fluoro-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
3-[5-Bromo-2-(4-methyl-piperazin-1-yl)-phenyl]-1-(2-fluoro-4-methoxy-phenyl)-propenone,
2-Dimethylamino-N-[3-(3-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-acryloyl)-phenyl]-acetamide,
10 3-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(3-dimethylaminomethyl-4-hydroxy-phenyl)-propenone,
3-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(4-hydroxy-phenyl)-propenone,
3-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(3-hydroxy-phenyl)-propenone,
15 3-[4-Bromo-2-(4-methyl-piperazin-1-yl)-phenyl]-1-(3-dimethylaminomethyl-4-hydroxy-phenyl)-propenone,
N-(3-{3-[4-Bromo-2-(4-methyl-piperazin-1-yl)-phenyl]-acryloyl}-phenyl)-2-dimethylamino-acetamide,
1-(2-Dimethylaminomethyl-phenyl)-3-[2'-methyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
20 1-(3-Dimethylaminomethyl-phenyl)-3-[2'-methyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
1-(3-Dimethylaminomethyl-4-hydroxy-phenyl)-3-[2'-methyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
25 1-(4-Hydroxy-phenyl)-3-[2'-methyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
1-(2-Fluoro-4-methoxy-phenyl)-3-[2'-methyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
2-Dimethylamino-N-(3-{3-[2'-methyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-acryloyl}-phenyl)-acetamide,
30 1-(3-Dimethylaminomethyl-4-methoxy-phenyl)-3-[2'-methyl-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,
1-(2-Dimethylaminomethyl-phenyl)-3-[2'-methoxy-3-(4-methyl-[1,4]diazepan-1-yl)-biphenyl-4-yl]-propenone,
1-(3-Dimethylaminomethyl-phenyl)-3-[2'-methoxy-3-(4-methyl-[1,4]diazepan-1-yl)-biphenyl-4-yl]-propenone,
35 3-[2'-Methoxy-3-(4-methyl-piperazin-1-yl)-biphenyl-4-yl]-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
1-(2-{[(2-Dimethylamino-ethyl)-methyl-amino]-methyl}-phenyl)-3-[2'-methoxy-3-(4-methyl-piperazin-1-yl)-biphenyl-4-yl]-propenone, and
40 1-{2-[(tert-Butyl-methyl-amino)-methyl]-phenyl}-3-[2'-methoxy-3-(4-methyl-piperazin-1-yl)-biphenyl-4-yl]-propenone,
1-(2-Dimethylaminomethyl-phenyl)-3-[5-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone,

and salts thereof.

17. A composition comprising a compound as defined in any of the claims 1-16 and a pharmaceutically acceptable carrier.

5

18. A compound as defined in any of claims 1-16 for use as a medicament.

19. Use of a compound as defined in any of the claims 1-16 for the preparation of a pharmaceutical composition for the treatment of bacterial infections in a mammal in need thereof.

10

20. The use according to claim 19, wherein the bacterial infection is associated with a bacteria selected from Gram-positive bacteria, Gram-negative bacteria, microaerophilic bacteria and anerobic bacteria.

15

21. The use according to claim 20, wherein the bacteria is a microaerophilic bacteria associated with gastric disease, such as *Helicobacter pylori*.

22. The use according to claim 20, wherein the bacteria is selected from antibiotic-sensitive and -resistant strains of *S.aureus*.

20

23. The use according to claim 20, wherein the bacteria is selected from antibiotic-sensitive and -resistant strains of *E.faecium*.

24. The use according to claim 20, wherein the bacteria is selected from a *S.pneumoniae* and *S.pyogenes*.

25

25. The use according to claim 20, wherein the bacteria is a member of *Enterobacteriaceae*, e.g. *E.coli*.

30

26. The use according to claim 20, wherein the bacteria is a pathogenic anaerobic bacteria, such as *Bacteroides fragilis* or *Clostridium species*.

27. Use of a compound as defined in any of claims 1-16, for the preparation of a pharmaceutical composition for the treatment of infections associated with protozoa in a mammal.

35

28. The use according to claim 27, wherein the infection is associated with a protozoa selected from *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae*.

40

29. Use of a compound as defined in any of the claims 1-16, for the preparation of a pharmaceutical composition for the treatment of infections associated with *Leishmania spp* in a mammal.

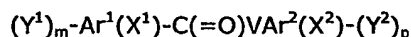
30. The use according to claim 29, wherein the infection is cutaneous and/or visceral.

31. A method of predicting whether a chemical compound as defined in any of the claims 1-16 has a potential inhibitory effect against a microorganism selected from *Helicobacter pylori* and *Plasmodium falciparum*, said method comprising preparing a mixture of a dihydroorotate dehydrogenase, a substrate for dihydroorotate dehydrogenase and the chemical compound, measuring the enzymatic activity of dihydroorotate dehydrogenase (A), comparing the enzymatic activity of dihydroorotate dehydrogenase (A) with the standard activity of dihydroorotate dehydrogenase (B) corresponding to the activity of a dihydroorotate dehydrogenase in a similar sample, but without the chemical compound, predicting that the chemical compound has a potential inhibitory effect against *Helicobacter pylori* and *Plasmodium falciparum* if A is significantly lower than B.

15

32. A process for preparation of a compound as defined in any of claims 1-16, and wherein V is -CH=CH-, comprising the steps

- (a) combining a ketone derivative of formula $(Y^1)_m-Ar^1(X^1)-C(=O)-CH_3$ with an aldehyde derivative of formula $HCO-Ar^2(X^2)-(Y^2)_p$ so as to form a mixture,
- (b) isolating a compound of the formula



33. The process of claim 32, wherein the mixture further comprises a suitable solvent.

25

34. The process according to any of claims 32-33, wherein the mixture further comprises a catalyst.

35. The process according to claim 34, wherein the catalyst is a base.

30

36. The process according to claim 34, wherein the catalyst is an acid.

37. A method for treating bacterial infections in a mammal comprising administration of a compound as defined in any of claims 1-16.

35

38. The method according to claim 37, wherein the bacterial infection is associated with bacteria selected from Gram-positive bacteria, Gram-negative bacteria, microaerophilic bacteria, and anaerobic bacteria.

39. The method according to claim 38, wherein the bacteria is a microaerophilic bacteria associated with gastric disease, such as *Helicobacter pylori*.

40. The method according to claim 38, wherein the bacteria is selected from antibiotic-sensitive and -resistant strains of *S.aureus*.

41. The method according to claim 38, wherein the bacteria is selected from antibiotic-sensitive and -resistant strains of *E.faecium*.

5 42. The method according to claim 38, wherein the bacteria is selected from *S.pneumoniae* and *S.pyogenes*.

43. The method according to claim 38, wherein the bacteria is a member of *Enterobacteriaceae*, e.g. *E.coli*.

10

44. The method according to claim 38, wherein the bacteria is a pathogenic anaerobic bacteria, such as *Bacteroides fragilis* or *Clostridium species*.

45. A method for treatment of infections associated with protozoa in a mammal
15 comprising administration of a compound as defined in any of claims 1-16.

46. The method according to claim 45, wherein the infection is associated with a protozoa selected from *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae*.

20

47. A method for treatment of infections associated with *Leishmania spp.* in a mammal comprising administration of a compound as defined in any of claims 1-16.

48. The method according to claim 47, wherein the infection is cutaneous and/or visceral.

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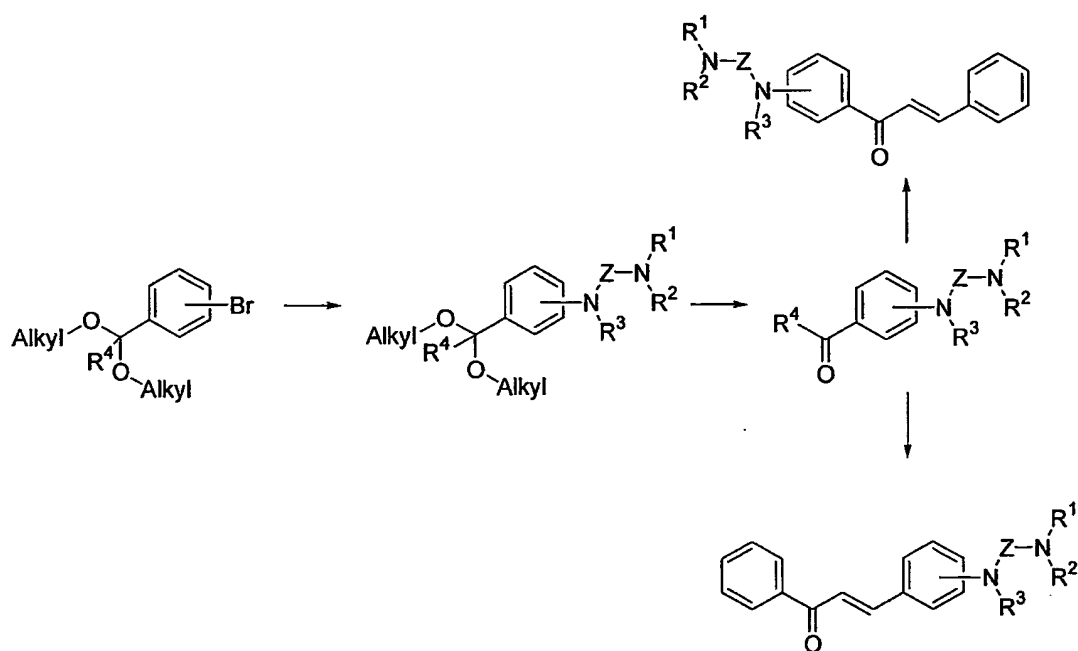


Fig. 1

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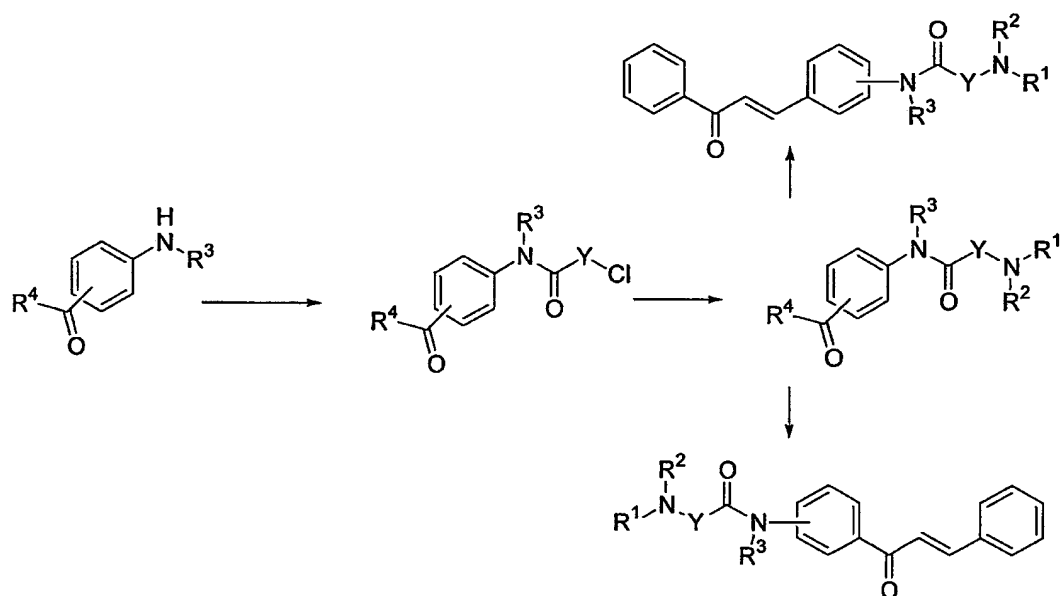


Fig. 2

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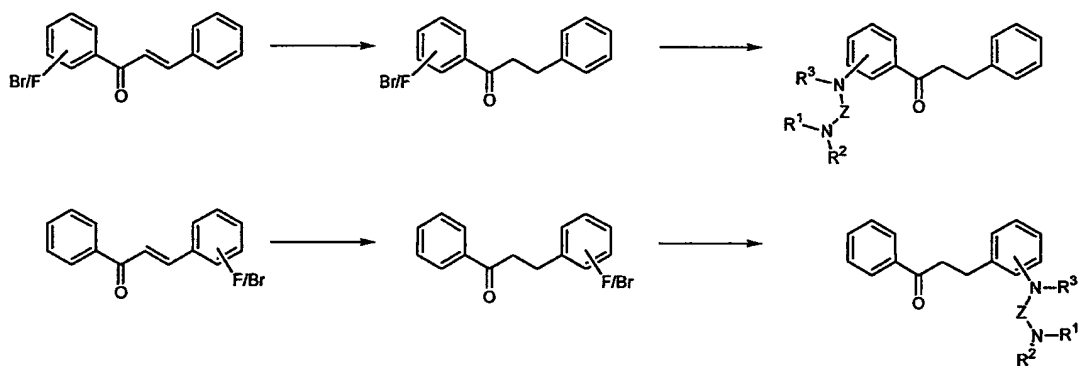


Fig. 3

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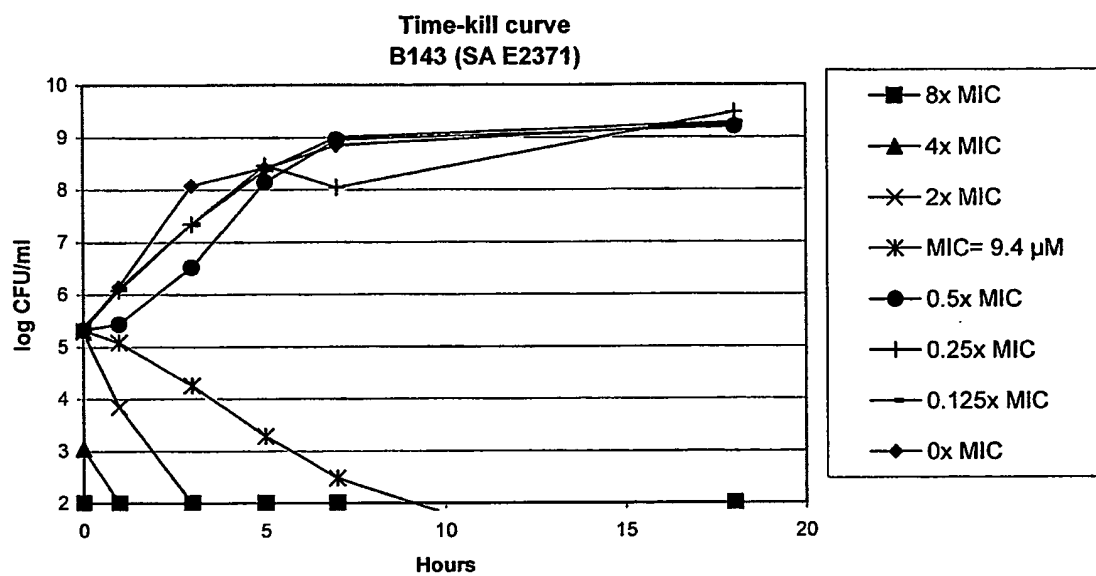


Fig. 4

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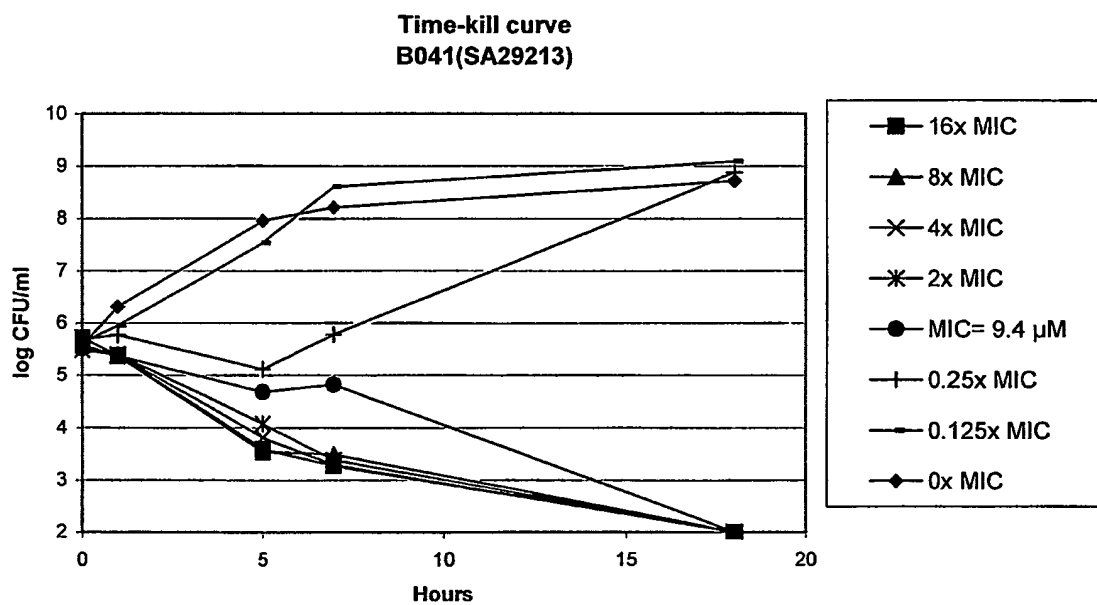


Fig. 5

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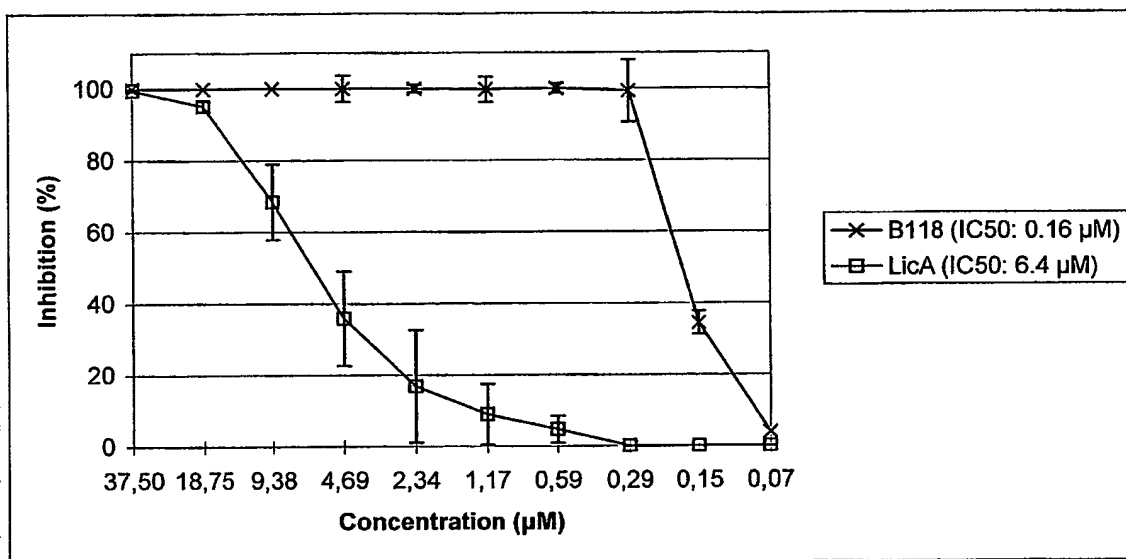


Fig. 6

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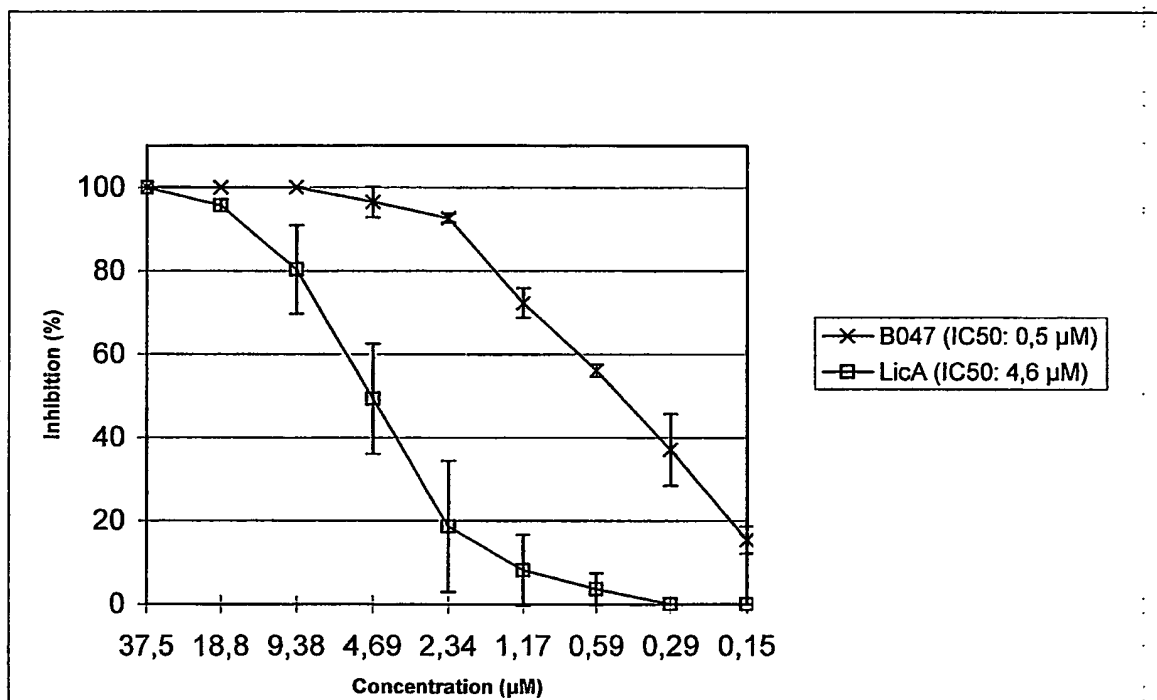


Fig. 7

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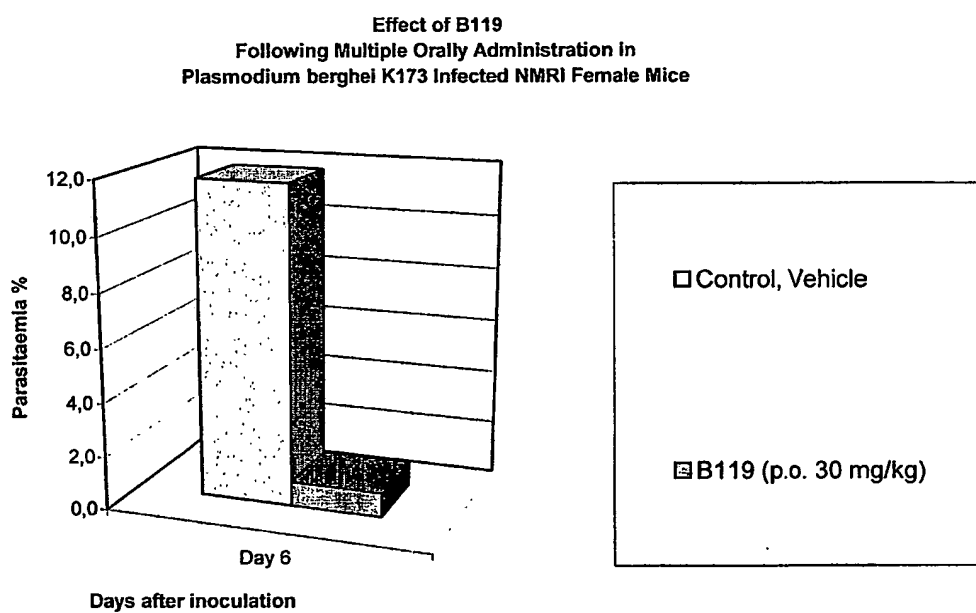


Fig. 8

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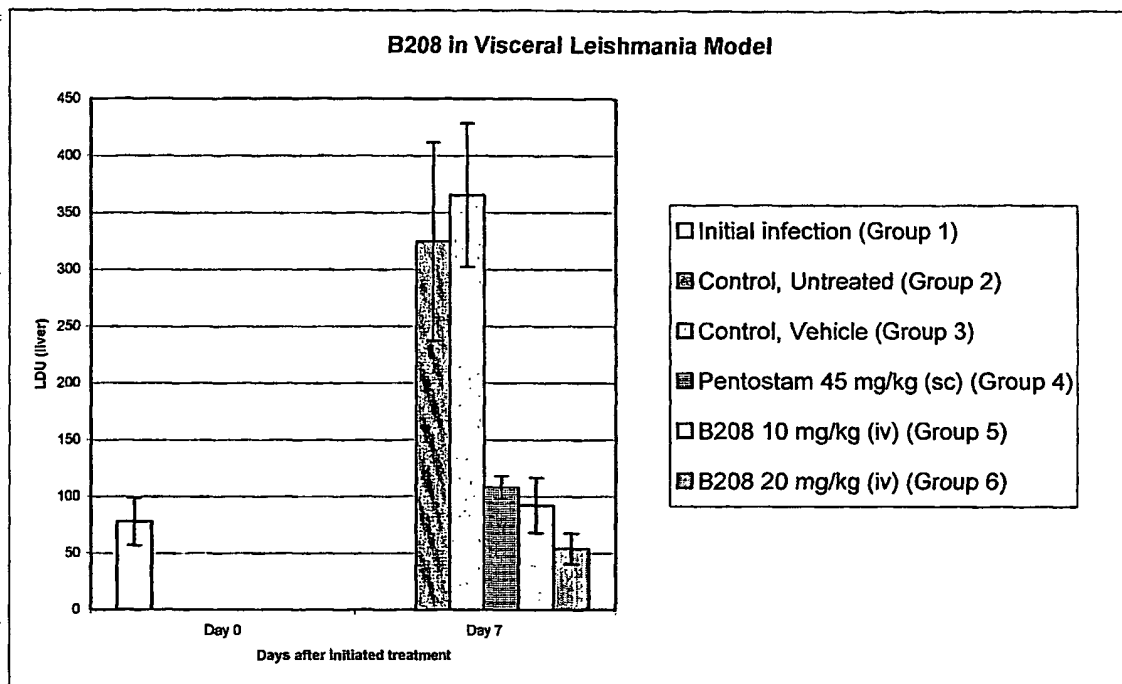


Fig. 9

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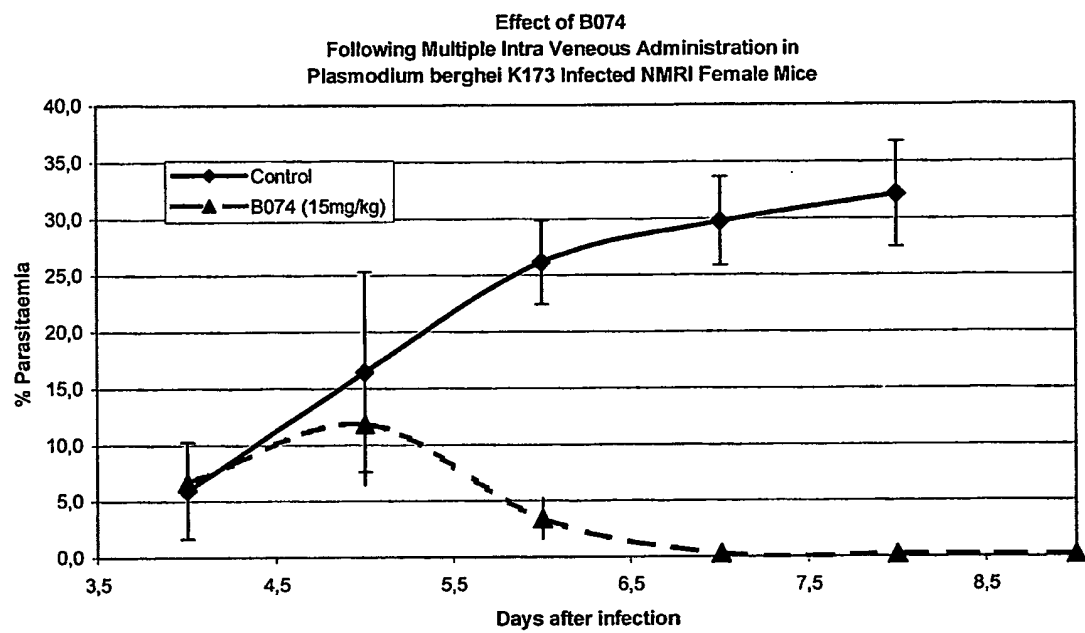


Fig. 10

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gade 9, P.O. Box 831, DK-2100 Copenhagen Ø (DK).

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(71) Applicant (*for all designated States except US*): **LICA PHARMACEUTICALS A/S** [DK/DK]; Fruebjergvej 3, DK- 2100 Copenhagen Ø (DK).

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(54) Title: **DIAMINO-FUNCTIONAL CHALCONES**

(57) Abstract: The invention provides novel diamino-functionalised chalcone derivatives and analogues thereof. Use of the compounds, or compositions comprising them, as pharmaceutically active agents, in particular against bacterial and parasitic infections, is also disclosed. The invention further relates to a method for detecting inhibitory effects against e.g., bacteria, parasites, fungi, and helminths. The chalcones of the invention carry amino substituents and exhibit enhanced biological effects combined with improved metabolic and physicochemical properties, making the compounds useful as drug substances, in particular as antiparasitic and bacteriostatic agents.

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INTERNATIONAL SEARCH REPORT

International Publication No
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A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07C225/22 A61K31/136 A61P31/04		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07C		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, CHEM ABS Data, WPI Data, BIOSIS, EMBASE, BEILSTEIN Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93 17671 A (STATENS SERUMINSTITUT) 16 September 1993 (1993-09-16) cited in the application page 88 page 97	1
A	WO 99 00114 A (CHRISTENSEN SOEREN BROEGGER ;STATENS SERUMINSTITUT (DK); KHARAZMI) 7 January 1999 (1999-01-07) cited in the application the whole document	1
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Date of the actual completion of the international search 18 December 2003		Date of mailing of the international search report 29/12/2003
Name and mailing address of the ISA European Patent Office, P.O. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Goetz, G

INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 03/00333

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DOSHI, RAJEEV ET AL: "Synthesis and biological evaluation of some novel isoxazoles and cyanopyridines, a new class of potential anti-tubercular agents"</p> <p>INDIAN JOURNAL OF CHEMISTRY, SECTION B: ORGANIC CHEMISTRY INCLUDING MEDICINAL CHEMISTRY (1999), 38B(3), 348-352 , vol. 38b, no. 3, 1999, pages 348-352, XP009019138</p> <p>the whole document</p> <p>-----</p>	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 03/00333

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 37 - 48 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/DK 03/00333

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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